EFFECTS OF EXERCISE ON COGNITIVE AND PHYSICAL FUNCTIONS IN INDIVIDUALS WITH PARKINSON'S DISEASE

by

MANUELA CRISTINA BARNA

(Under the Direction of Michael Horvat)

ABSTRACT

Introduction. Parkinson's disease (PD) is characterized by progressive loss of motor function, followed by behavioral, physiological, and cognitive modifications in a great proportion of patients. Exercise is considered a valuable tool in improving or delaying the progression of motor and cognitive aspects of the disease. However, the optimal delivery content of exercise for people with PD has not been identified yet. The purposes of this study were to compare two groups of individuals with PD without dementia on: 1) executive function following 12 weeks exercise intervention at two different frequencies; and 2) physical function as measured by the Short Physical Performance Battery (SPPB), following 12 weeks of exercise training at two different weekly frequencies. **Methods.** Twenty three individuals (mean age = 68.60 yr. ± 5.8 yr.) with stage 2 - 3 PD without dementia that exercised 4 - 5 times per week were compared to twenty individuals with PD without dementia (mean age = 67.65 yr. ± 4.5 yr.) that exercised three times or less each week. **Results.** N-back response time data were analyzed through a mixed factorial ANOVA with time and load as the within – subjects factors. Results indicated a significant interaction between time and group, F (1, 41) = 14.96, $p < .001$,

$\eta_p^2 = 0.26$ suggesting an improvement in working memory response time for participants in the high - frequency group following the exercise intervention. Global switch costs data were analyzed through a mixed factorial ANOVA with time as the within – subjects factor. Results revealed a significant interaction between time and group F (1, 41) = 5.53, $p < .05$, $\eta_p^2 = 0.09$, with the high – frequency group showing smaller switch costs after the exercise. Also, analyses revealed a significant interaction between time and group for the SPPB summary scores, F (1, 41) = 8.37, $p < .05$, $\eta_p^2 = 0.17$. **Conclusions.** These findings indicate that changes in executive and physical functions in individuals with early – moderate Parkinson's disease depend on a specific frequency of exercise, with higher frequencies triggering more benefits than lower ones. Future research should focus on identifying the types and frequencies of exercise with the most promising effects for this population.

INDEX WORDS: Parkinson's disease, Exercise Frequency, Working Memory, Cognitive Flexibility, Physical Function.

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MANUELA CRISTINA BARNA

B.S., Transilvania University, Brasov, Romania, 2008

M.Ed., Babes-Bolyai University, Cluj-Napoca, Romania, 2009

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MANUELA CRISTINA BARNA

Major Professor:	Michael Horvat
Committee:	Philip Tomporowski Kathy Simpson Joe Nocera

Electronic Version Approved:

Julie Coffield
Interim Dean of the Graduate School
The University of Georgia
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DEDICATION

To my husband, Dr. Adrian Caciula, for all his love, patience, and support.

To my baby, Andrei, for making my life joyful every day.

To my parents, who gave their best for my best!

To my brother who always believed in me.

To my parents – in law, sisters – in law, and brother in law for their continuous encouragement and eager support.

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CHAPTER 1

INTRODUCTION

Parkinson's disease (PD) is characterized by progressive loss of motor function, followed by behavioral, physiological, and cognitive modifications in a great proportion of patients. According to National Parkinson Foundation, almost 1.5 million Americans currently have the disease, every 9 minutes, someone in the US is diagnosed with PD, and 60,000 new cases are reported every year. The incidence of PD increases rapidly over the age of 60, with only 4% of the total cases being identified under the age of 50. As for the men-women ratio, it is suggested that men are one and a half times more predispose to developing PD than women (Van Den Eeden et al., 2003).

The specific cause of PD may be an imbalance of chemical messengers in the brain (Stewart A. Factor, 2002). The primary messenger affected in PD is the neurotransmitter called dopamine, concentrated in the substantia nigra of the midbrain. When neurons in the substantia nigra degenerate, the resulting loss of dopamine (DA) causes the nerve cells of the striatum to fire excessively. This makes it difficult to control movements, and primary motor symptoms associated with PD, including: 1) Resting tremor (although one in four patients does not have shaking as a primary characteristic; 2) Muscle rigidity (increased muscle tone and stiffness); 3) Bradykinesia (slowness of movement); and 4) Postural instability (loss of ability to maintain an upright stance), all of which decrease the functional ability in the disease. In addition to motor dysfunction, recent neuropsychological studies also suggest that cognitive limitations are associated with dopamine depletion within the caudate nucleus (Lewis et al., 2003). It has been

documented in PD, that dopamine depletion is restricted in the earlier stages to the putamen and the dorsal caudate nucleus, and only later progresses to the more ventral parts of the striatum and the mesocorticolimbic dopaminergic system (Cools, Barker, Sahakian, & Robbins, 2001).

Cognitive function impairments are observed relatively early after the onset of PD and if not treated accordingly, can progress to dementia (Bassett, 2005). People report feeling disorganized and distracted, or having difficulties planning and carrying through tasks. They may also feel challenged by situations that divide their attention or that require them to remember information. It is estimated that 80% of PD patients will manifest cognitive impairments, including dementia, through the course of the disease that will affect their quality of life, and will interfere with occupational and social functioning (Emmanuelle Silva Tavares Sobreira1, José Humberto Silva Filho2, & Vitor Tumas4, 2008). It is becoming more evident that cognitive deficits are common in non-demented PD patients, and that mild cognitive impairment (MCI) is an early indicator of dementia in PD (Pagonabarraga et al., 2008). It was once thought that PD patients would experience cognitive changes only in the mid-to-late stages of the disease, but more recent research suggests that mild changes can show up as early as the time of diagnosis (Aarsland et al., 2010).

Until recently, treatment options of cognitive dysfunction were based primarily on patient and family education, behavioral interventions, and the use of cholinesterase inhibitors (Bassett, 2005). These treatments sought mainly to avoid deterioration of organizational skills, attention and concentration that could affect patient's social, intellectual, and occupational activities. In contrast, little attention was given to the effects of exercise on motor and cognitive function of people with PD. The inclusion of

exercise interventions suggest that exercise is an adjunctive strategy in early and advancing PD, and that exercise will have positive effects on both motor and non-motor signs and symptoms of PD (Alberts, Linder, Penko, Lowe, & Phillips, 2011; K. E. Cruise et al., 2011; A. L. Ridgel, C. H. Kim, E. J. Fickes, M. D. Muller, & J. L. Alberts, 2011; Rodrigues-de-Paula F, 2011). Exercise is considered an effective component of protective therapy in PD, and could possibly slow the rate of progression of the disease (Rodrigues-de-Paula F, 2011; Rodrigues de Paula, Teixeira-Salmela, Coelho de Morais Faria, Rocha de Brito, & Cardoso, 2006). To date, no research has been uncovered that examines the impact of community based exercise on the executive function and working memory of people with PD, and is the focus of this investigation.

Statement of the problem:

People with PD experience a myriad of physical and mental symptoms that evolves into cumulative and progressive disability, with a large percentage of people with PD eventually becoming functionally disabled. According to Parkinson's disease Foundation, only in the United States the direct and indirect costs linked to PD are estimated to be nearly $25 billion per year, including treatment, social security payments and lost income from inability to work. Parkinson's disease causes impaired mobility and functionality that inhibits or discourages activities of daily living. Also, it is becoming evident that people at early or moderate stage of PD tend to become less physically active, and reduce the amount of exercise, compared with asymptomatic individuals at the same age (M. A. Hirsch & Farley, 2009). The lack of activity is considered an important factor in accelerating the degenerative process of PD in cognitive and motor functions. Although medication partially controls the motor symptoms, it has been

suggested that adding daily exercise and activity will enhance drug's beneficial effects (Tillerson, 2003).

Cognitive dysfunction accentuates considerably the disability and caregiver strains, and also affects the quality of life over the course of the disease (Schrag, Jahanshahi, & Quinn, 2000). According to Beato et al. (2008), alteration of working memory could be partly responsible for the executive function impairments encountered in people with PD. Working memory is defined as the ability to temporarily store and manipulate information, rather than simply repeat it. The use of working memory is important in planning, problem solving and independent living. Exploring the effects of exercise training on the cognitive and motor functions in people with PD is important for determining the efficacy of exercise as an adjuvant and protective therapy for delaying the disease progression. Also, by identifying the effects of different frequencies of weekly exercise for people with PD can help develop more specialized exercise intervention strategies for successfully managing the disease.

Study Purpose:

The purpose of this investigation is to identify the effects of different frequencies of 12 weeks of community based exercise training on working memory and cognitive flexibility in individuals with PD, and also to determine the effects of exercise on their physical function.

Study Aims: The specific aims of this study are:

Aim 1: To determine whether 12 weeks of high - frequency exercise training will modify *aspects of executive function* in individuals with idiopathic PD without dementia, stages II-III as determine by Hoehn and Yahr scale.

Aim 2: To determine whether 12 weeks of high – frequency exercise training will significantly modify *physical function* in individuals diagnosed with idiopathic PD without dementia, stages II-III as determine by Hoehn and Yahr scale.

Aim 3: To determine the relationship between changes in walking speed and changes in executive function following 12 weeks of multimodal exercise training at different frequencies.

Hypotheses:

The research hypotheses for this study are:

Hypothesis 1: We hypothesize that 12 weeks of high- - frequency exercise training as opposed to low – frequency exercise training will significantly improve aspects of working memory and shifting in individuals with stage II-III Parkinson's disease, without dementia.

Hypothesis 2: Individuals with PD that will participate in high – frequency exercise training for 12 weeks will significantly improve physical function compared to individuals with PD that will participate in law – frequency exercise training.

Hypothesis 3: Changes in walking speed after 12 weeks of high – frequency exercise training will statistically significantly predict changes in executive function in non – demented individuals with PD.

Rationales:

Rationale 1: Working memory is one aspect of cognitive function that tends to deteriorate in people diagnosed with PD and, as the disease progresses, interfere with individual's mobility and activities of daily living by lowering their psychomotor speed (Koerts, Van Beilen, Tucha, Leenders, & Brouwer, 2011). Acute bouts of aerobic

exercise has been shown to be beneficial for healthy adults, improving different aspects of cognition such as speed of processing (Barella, Etnier, & Chang, 2010; P. D. Tomporowski, 2003), selective working memory (Benjamin A. Sibley, 2007; Pontifex, Hillman, Fernhall, Thompson, & Valentini, 2009), and sensory processes (Lambourne, Audiffren, & Tomporowski, 2010). Chronic aerobic exercise has been shown to improve cognition in parkinsonian animal models, as well as in human participants (J. E. Ahlskog, 2011). Besides, Chen et al. (2005) suggest that participation in higher levels of physical activity during early adulthood may lower the risk of PD. The changes in cognition are linked to enhanced neuroplasticity, exercise-related protection from dopaminergic neurotoxins, and increased neurotrophic factor expression (J. E. Ahlskog, 2011). Benjamin and his colleagues' findings (2007) suggest that people with generally lower cognitive performances tend to benefit more from exercise interventions. Since cognitive dysfunction is one of the major non-motor features of PD we expect exercise training to improve selective aspects of cognition, such as working memory.

Rationale 2: The progressive decline of cognitive function in people with PD leads to deterioration of individual's functionality and quality of life. The major aspect of daily living that becomes impaired is walking, which initially was considered an automatic motor function with little implication of higher mental circuits. However, walking and mobility are more often linked to cognitive function, and specifically to executive function (ref.). Older adults and PD people with poor executive function tend to walk slower, have increased gait variability, fall more often, and perform poorly on complex mobility tasks such as rising from a chair and dual tasking (Kelly, Eusterbrock, & Shumway-Cook, 2012; Persad, Jones, Ashton-Miller, Alexander, & Giordani, 2008).

Following twelve weeks of exercise training intervention we expect people with PD to show an increase in overall physical function.

Significance of the study:

Parkinson's disease is a neurodegenerative disorder that has been studied in the past decades and has been associated with motor and non-motor symptoms that contribute to reduced quality of life and independence. Most of the treatment options focus on the motor aspects of PD (and are largely pharmacologically based), while a minimum amount of attention is given specific to the deterioration of cognitive function. Considering the great impact of an impaired cognition on the mobility and quality of life of people living with PD, effective strategies to stop or delay the regression of intellectual function are greatly needed.

Delimitations of the study:

This study is limited to measures of executive function through the use of the N-back task and the auditory switch task. Physical function will be measured using the Short Physical Performance Battery which includes repeated chair stands, balance testing, and 8' walk. Also, this study is limited to individuals with PD that participate with regularity in exercise classes, and thus we do not have a non – exercise control group.

Definition of terms

Terms described in the following section are defined as conceptual, referring to concepts that have been previously defined and accepted by recognized experts and authorities.

Activities of Daily Living (ADL): Term used to describe activities related to independent living and include preparing meals, managing money, shopping for groceries or personal items, performing light or heavy housework, and using a telephone.

Aerobic exercise: is physical exercise of relatively low intensity that depends primarily on the aerobic (with oxygen) energy-generating process (Sharon et al., 2007).

Acute exercise: is a single, relatively short bout of exercise (Buckworth, et al., 2013).

Akinesia: is the inability to initiate movement due to difficulty selecting and/or activating motor programs in the central nervous system.

Basal Ganglia: Four masses of gray matter located deep in the cerebral hemispheres that secrete acetylcholine, dopamine, GABA, and serotonin and contribute to some of the subconscious aspects of involuntary movement (Thomas, 1997).

Bilateral: Pertaining to two sides of the body (Anschel et al., 1991)

Bradykinesia: Describes difficulty in initiating movement and slowness of movement.

Chronic exercise: is exercise carried out repeatedly over time, usually several times each week for various durations (Buckworth, et al., 2013).

Cognitive function: refers to a group of mental processes that includes attention, memory, producing and understanding language, learning, reasoning, problem solving, and decision making.

Dopamine: A catecholamine neurotransmitter, or brain messenger, implicated in some forms of psychosis and abnormal movement disorders (Thomas, 1997).

Dyskinesia: Condition characterized by motor restlessness, abnormal facial movements, and involuntary jerky or writhing movements (Anschel et al., 1991).

Dysphagia: The inability to swallow or difficulty in swallowing (Thomas, 1997).

Idiopathic: Relates to an unknown cause of disability or morbidity (Anschel et al., 1991).

Parkinson's disease: A chronic nervous system disease characterized by a fine, slowly spreading tremor, muscular weakness and rigidity, and a peculiar gait (Thomas, 1997).

Physical Function: is defined as one's ability to carry out various activities, ranging from self-care (activities of daily living) to more challenging and vigorous activities that require increasing degrees of mobility, strength or endurance (Stewart et al., 1992).

Postural instability: is defined as the loss of ability to maintain an upright stance.
Rate of perceived exertion (RPE): A subjective way to measure exercise intensity using numbers on a scale representative of the effort level.

Quality of life: references the general well-being of individuals and societies and include not only wealth and employment, but also the built environment, physical and mental health, education, recreation and leisure time, and social belonging (Gregory et al., 2009).

Rigidity: Refers to difficulty with initiating movement, continuous muscle tension, and uncoordinated reciprocal muscle groups (Anschel et al., 1991).

Substantia nigra: Largest nuclear mass of the midbrain containing neurons filled with melanin accounting for its black color (Young and Young, 1997).

Tremor: Involuntary, rhythmic, alternating bursts of movement of antagonistic muscle groups (Anschel et al., 1991).

Working memory: is a system for temporarily storing and managing the information required to carry out complex cognitive tasks such as learning, reasoning, and comprehension (A. Baddeley, 1992).

CHAPTER 2

REVIEW OF THE LITERATURE

Introduction. This chapter will present a review of the current literature regarding the neurphysiological and behavioral underlying mechanisms of Parkinson's disease. Particular aspects of physical and cognitive function of the disease will also be outlined. Besides, the types of interventions presently considered as being effective means to improve the debilitating progression of PD, and the effects of exercise on physical and cognitive function of the disease will be exposed in the last part of the chapter.

Neurophysiology of PD

Parkinson's disease is the second most common chronic neurological disease that affects not only the patients' lives, but also the society in which they live (Lau L.M., 2006; Weintraub D, 2008). At neurochemical level, the disease presents a lack of balance in the dopaminergic pathway, which is responsible for the connection between substantianigra and the striatum (Agid, 1991). The *substantianigra* is a brain structure located in the mesencephalon (midbrain) that plays an important role in reward, addiction, and movement. Substantianigra is Latin for "black substance", reflecting the fact that parts of the substantianigra appear darker than neighboring areas. This is due to high levels of melanin in dopaminergicneurons. Parkinson's disease is characterized by the death of dopaminergic neurons in the substantianigrapars compacta. The pars compacta serves mainly as an input to the basal ganglia circuit, supplying the striatum with dopamine. The *striatum* represents the major input station of the basal ganglia

system, and in turn receives input from the cerebral cortex. PD results in loss of dopaminergic innervation to the striatum (and other basal ganglia). Besides the loss of dopaminergic neurons, PD is characterized by the presence of intracytoplasmic inclusions called Lewy bodies (Lang AE, 2004).

The dopaminergic neurons project to the striatum and their loss leads to alterations in the activity of the neural circuits within the basal ganglia that regulate movement, in essence an inhibition of the direct pathway and excitation of the indirect pathway. The direct pathway facilitates movement and the indirect pathway inhibits movement, thus the loss of dopamine cells leads to a hypokinetic movement disorder. The lack of dopamine results in increased inhibition of the ventral anterior nucleus of the thalamus, which sends excitatory projections to the motor cortex, thus leading to hypokinesia. There are four major dopamine pathways in the brain; the nigrostriatal pathway, referred to above, mediates movement and is the most conspicuously affected in early Parkinson's disease. The other pathways are the mesocortical, the mesolimbic, and the tuberoinfundibular. Disruption of dopamine along the non-striatal pathways likely explains much of the neuropsychiatric pathology associated with Parkinson's disease.

The mechanism by which the brain cells in Parkinson's are lost may consist of an abnormal accumulation of the protein alpha - synuclein bound to ubiquitin in the damaged cells. The alpha – synuclein - ubiquitin complex cannot be directed to the proteosome. This protein accumulation forms proteinaceous cytoplasmic inclusions called Lewy bodies. The latest research on pathogenesis of disease has shown that the death of dopaminergic neurons by alpha-synuclein is due to a defect in the machinery that transports proteins between two major cellular organelles — the endoplasmic reticulum

(ER) and the Golgi apparatus. Certain proteins like Rab1 may reverse this defect caused by alpha-synuclein in animal models.

Excessive accumulations of iron, which are toxic to nerve cells, are also typically observed in conjunction with the protein inclusions. Iron and other transition metals such as copper bind to neuromelanin in the affected neurons of the substantianigra. Neuromelanin may be acting as a protective agent. The most likely mechanism is generation of reactive oxygen species. Iron also induces aggregation of synuclein by oxidative mechanisms. Similarly, dopamine and the byproducts of dopamine production enhance alpha-synuclein aggregation. The precise mechanism whereby such aggregates of alpha-synuclein damage the cells is not known. The aggregates may be merely a normal reaction by the cells as part of their effort to correct a different, as-yet unknown, insult. Based on this mechanistic hypothesis, a transgenic mouse model of Parkinson's has been generated by introduction of human wild-type alpha-synuclein into the mouse genome under control of the platelet-derived-growth factor-β promoter.

A recent view of Parkinson's disease implicates specialized calcium channels that allow substantianigra neurons, but not most neurons, to repetitively fire in a "pacemaker" like pattern. The consequent flooding of calcium into these neurons may aggravate damage to mitochondria and may cause cell death. One study has found that, in experimental animals, treatment with a calcium channel blocker isradapine had a substantial protective effect against the development of Parkinson's disease.

It is increasingly clear that there are many parallel circuits within the basal ganglia, each subserving a different function and each modulated by DA. Thus, it is

reasonable to predict that patients will have a wide variety of dysfunctions extending well beyond the classic motor disabilities associated with the disease. Indeed, patients with Parkinson's disease appear to be at increased risk for a variety of cognitive and psychiatric dysfunctions. Most common is dementia and depression. However, hallucinations, delusions, irritability, apathy, and anxiety also have been reported.

Besides, it is believed that almost 30% of PD patients suffer changes in executive function, which are skills that involve planning and execution of daily activities, such as task initiation, attention, abstraction ability, concentration, flexibility, planning, and selectivity of stimuli, self-control, mental control, working memory, and impulse inhibition. Until recently, treatment of cognitive dysfunction in PD was based primarily on patient and family education, behavioral interventions, and the use of cholinesterase inhibitors (Bassett, 2005).

For many years, little attention was given to the effects of exercise on motor and cognitive function of people with PD, due to the lack of evidence and measurable results in this non-pharmacological approach. At the present time, benefic effects of exercise on cognitive function have been demonstrated in animal models, and also in a large number of clinical studies with older adults(Erickson & Kramer, 2009; Kramer, Erickson, & Colcombe, 2006). The cognitive-related benefits in animals include favorable influence on neuronal survivability and function, neuroinflamation, and neuroendocrine response to stress (Baker et al., 2010). Physiological processes, such as glucoregulation and cardiovascular health are also positively influenced by exercise. When these functions are impaired, the risk of developing cognitive impairment and neurodegenarative diseases is greatly increased (Baker et al., 2010).

Even though the exact cause of PD has long been debated, and the specific etiology still remains unknown, two factors are thought to influence the disease: genetic and environmental factors. Understanding the cause of PD is critical as that knowledge could lead to directed research that will develop new and potent therapies. In the following section we will discuss, in more detail, the two hypothesis that have been developed for a better understanding of the underlying events that lead to the development of this neurodegenerative disease.

The genetic hypothesis is formed based on the association of specific types of genes with PD abnormalities. These genes appear to play a major role in the labeling of proteins for break down (8), and also to affect the response to oxidative stress. Three genes have been found to be associated with inherited PD: α-synuclein, parkin, and UCH-L1 (7–9). α - Synuclein is a small protein of 140 amino acids that was first identified in the Pacific electric ray, Torpedo californica (Maroteaux L, 1988). Mutations in the α-synuclein gene have not been identified in patients with sporadic PD, but immunocytochemistry has demonstrated that α-synuclein is an abundant component of Lewy bodies, even in patients with familial or sporadic PD who do not have the gene mutation (Spillantini MG, 1997).This suggests that accumulation of α-synuclein may be central to the development of PD. Lewy bodies are usually observed within the cell soma, but also can be seen in neurites or free in the extracellular space. Lewy bodies are commonly observed in the brain regions showing the most neuron loss in PD, including SN, locus coeruleus, the dorsal motor nucleus of the vagus, and the nucleus basalis of Meynert, but they are also observed in neocortex, diencephalon, spinal cord, and even peripheral autonomic ganglia.

The environmental toxin hypothesis rely strongly on the discovery of the neurotoxin 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP). MPTP is a byproduct of the illicit manufacture of a synthetic meperidine derivative. Drug addicts who took MPTP developed a syndrome that strikingly resembled PD, both clinically and pathologically (Langston et al 1983). Exogenous toxins have been found to exert symptoms like those found in PD patients. This led to the study of herbicides and insecticides as possible causes for PD; as they behave similarly to MPTP and act as poisons in the environment. According to the environmental toxin hypothesis, exposure to well water, pesticides, herbicides, industrial chemicals, wood pulp mills, farming, and living in a rural environment may represent risk factors in developing PD (Agid, 1991).

Parkinson's disease: a progressive disorder

PD invariably progresses with time. The Hoehn and Yahr scale, which defines five stages of progression, is commonly used to estimate the evolution of the disease. This scale was first published in 1967 in the journal Neurology by Melvin Yahr and Margaret Hoehn. However, not all patients initially experience all of the common motor signs of the disorder, which are: tremor at rest, rigidity, bradykinesia (slowing of movement), and postural instability. Motor weakness or stiffness is commonly one of the first symptoms that show up, and it is not always diagnosed correctly. Usually, specialists use medical history and neurological examination to get the clinical diagnosis, since there is no laboratory tests that can help establish an accurate diagnosis.

Even neuroimaging, which is helpful in estimating dopaminergic loss is sometimes imperfect, and it is also too expensive to be used as a routine tool for PD diagnosis. Patients may be given levodopa and resulting relief of motor impairment tends

to confirm diagnosis. The finding of Lewy bodies in the midbrain on autopsy is usually considered proof that the patient suffered from Parkinson's disease. The progress of the illness over time may reveal it is not Parkinson's disease, and some authorities recommend that the diagnosis be periodically reviewed.

Physical Function in PD

Parkinson's disease (PD) is a movement disorder caused by an imbalance of chemical messengers in the brain. The primary messenger affected in PD is the neurotransmitter called dopamine, concentrated in the substantia nigra of the midbrain; the shortage of dopamine creates the marks and symptoms typical of PD.

Distinctive features of PD have been mentioned first in 1817 in the seminal work of James Parkinson's, ―An Essay on the Shaking Palsy" (Parkinson & Library, 1817). At that time he presented a descriptive account and discussion of 6 individuals with, what he termed, Paralysis Agitans (Shaking Palsy). According to his observations, Paralysis Agitans is a four stages progressive disease: the first stage is characterized by a slight weakness and trembling, sometimes in the head, but more frequently in one of the hands. The symptoms appear to increase progressively, and after a period of 12 months both sides of the body are affected, and tasks such as writing, pointing, and reading become very difficult to achieve. In stage 2, individuals encounter postural instability and leg trembling, difficulties that will gradually diminish their desire to walk. In stage 3, an increased forward lean can be observed, and the walking pattern looks more like running because the individuals are forced to walk on their toes. Besides, they begin having sleep disturbances, difficulties feeding themselves, and problems speaking clearly. The fourth stage of Paralysis Agitans is characterized by violent and unceasing tremors even while

sleeping, head dropping with the chin touching the sternum, delirious moments, lack of speaking, and abnormal bowel movements.

It was not until the late 19th century that Jean Charcot, after a long period of careful patient examination, renamed paralysis agitans, Parkinson's disease, primarily because he observed that individuals do not present the muscle weakness encountered in paralysis. Few years later, Charcot and his colleagues established the 4 cardinal characteristics of Parkinson's disease: 1) Resting tremor (although one in four patients does not have shaking as a primary characteristic; 2) Muscle rigidity (increased muscle tone and stiffness); 3) Bradykinesia (slowness of movement); and 4) Postural instability (loss of ability to maintain an upright stance). In 1959, Arvid Carlsson made the greatest medical breakthrough in Parkinson's disease, identifying that the reduction in the number and function of dopaminergic cells within the substantianigra was the cause of physical and pathological consequences which were observed previously. The addition of akinesia (poverty, or loss of control of voluntary movement) to bradykinesia, postural instability, rigidity, and tremors or uncontrolled shaking completed the physical hallmarks of the disease (Brown & Marsden, 1990; Rosenbaum, 2006; Sohn, 2003).

Tremor is the most common feature of the disease, but around 30% of individuals with PD do not have it at disease onset, and most of them develop it as PD progresses in time. Tremor can usually be observed when the limb is at rest, and tends to disappear when the individual performs voluntary movements or during sleep. In stage I, the tremor is unilateral (appears in only a single arm or leg), with stage II bringing bilateral involvement. The tremor in the hand has the aspect of a circular movement, with the

index finger touching the thumb like in –pill-rolling" (earlier pharmaceutical technique of manually making pills), and has a frequency of 4 and 6 hertz (cycles per second).

Slowness of movement or bradykinesia is another dominant feature that can be observed in people with PD, and it is characterized by difficulties in planning, initiating, and executing the movement (Berardelli, Rothwell, Thompson, & Hallett, 2001). Bradykinesia can be first observed while performing daily activities that require fine motor control such as writing, sewing, or getting dressed (Brooks, 2000). Sequential and simultaneous movements are compromised, thus making bradykinesia the most disabling symptom of the early stages in PD. Slowness of movement does not have an equal manifestation for all movements, but rely greatly on the emotional state or type of activity being initiated. Usually patients with PD perform better when some sort of external cues are provided (Nieuwboer et al., 2007), as it can be observed in cases where individuals are barely able to walk, but they can satisfactory ride a bike.

Muscle rigidity or stiffness is characterized by exaggerated and constant muscle contraction, and by increased muscle tone. Sometimes the rigidity can be uniform (lead-pipe rigidity) or ratchet (cogwheel rigidity), which is caused by the combination of tremor and increased muscle tone. Rigidity does not have a symmetrical manifestation in early stages of the disease, with the neck and shoulder muscles being the first body parts affected, followed by the face and extremities. In the late stages of PD, the whole body is affected by joint pain and rigidity, leading to a reduced ability to move.

Postural instability can usually be observed in the late stages of the disease, and it is the leading cause of poor balance and frequent falls. The high predisposition to falls

increases the risk for bone fractions (Sato, 2001). In the early stages of the disease, patients do not experience postural instability, especially if young ages of onset.

However, not all persons diagnosed with PD have all the hallmark features mentioned above. Other common signs that may be present include: handwriting changes, becoming cramped and small (micrographia); diminished facial expression (~~–m~~asked faces"); lowered voice volume or hoarseness (dysarthria); stopped posture; decreased arm swing on the affected side; changes in gait (walking), including shuffling of feet, short steps, and difficulty with turns.

In 1967, Margaret Hoehn and Melvin Yahr (Hoehn & Yahr, 1967) provided an emblem scale consisting of 5 stages to more accurately classify individuals with PD and to track disease progression. According to their observations, stages I and II are considered to be minimally disabled; stage III requires more service due to the predisposition to falling, while stages IV and V are severely disabled.

Hence, tremor at rest, rigidity, bradikinesia, and abnormalities of posture, gait, and balance are the cardinal manifestations of idiopathic PD. A neurologic examination is required for an accurate identification of these signs and for a correct diagnosis.

Exercise and Physical Function in PD

In general, individuals with disabilities tend to become less physically active than their non-disabled peers (M. A. Hirsch & Farley, 2009). In Parkinson's disease, studies have suggested the same tendency, with individuals at an early and moderate stage of the disease having a greater reduction in physical activity level than asymptomatic individuals of the same age. Furthermore, inactivity is considered an important factor in

accelerating the degenerative process of PD (Tillerson, 2003). Recent reviews and meta-analysis suggest that exercise is an adjunctive strategy in early and advancing PD (Olanow, Watts, & Koller, 2001), and that exercise has positive effects on both motor and non-motor signs and symptoms of PD. Exercise is a component of protective therapy in PD, and it is an effective strategy to slow the rate of progression or even prevent future progression.

Participating in regular physical activity has a preventive effect for individuals both before and after being diagnosed with PD. Studies have shown that moderate and high levels of physical activity lowers the risk of developing PD (Chen et al., 2005), and also suggested that participating with regularity in exercise programs can postpone the onset of the disease (Tsai et al., 2002).

Specialists became interested in analyzing various types of exercise and interventions strategies, designed to improve patient's mobility, muscular strength (Dibble et al., 2006), balance (M. Hirsch, Toole, Maitland, & Rider, 2003), aerobic conditioning, and gait (Nieuwboer et al., 2007). The results of these studies provided a body of evidence to support the notion that aerobic, resistance and flexibility exercises are beneficial for those suffering of PD. Moreover, Koller et al. (2001) recommended to healthcare providers to strongly encourage their patients to perform *"stretching, walking, swimming, or any activity the patient enjoys and will do regularly. More formal cardiovascular programs are also beneficial…"* The same specialists recommended for patients in early stages to perform *"strengthening with light weights"*, and for those in advanced stages ~~–to~~ *walk as much as several miles a day, if possible, or swim regularly"*(Olanow et al., 2001).

Studies conducted by Fisher, Petzinger and their colleagues (2008; 2007) indicated that exercise positively influence and regulate the activity of brain circuitry responsible for the control of movement in individuals with PD. Besides, it is thought that intensive exercise could improve the dopamine signaling in individuals with PD, and also change the blood flow in their brains. Increased blood flow will eventually augment the delivery of oxygen, help remove the waste materials, and accelerate the metabolic demands in the brain regions exposed to plasticity due to engaging in innovative experiences like exercise. These findings explain, in part, the underlying physiological mechanisms responsible for the promising results observable in PD people who participate in exercise intervention studies.

In 2010 the American College of Sports Medicine (ACSM) and the American Heart Association published, in *Healthy People 2010,* few exercise recommendations for adults, based on scientific evidence that regular exercise maintain or increase cardiovascular conditioning, muscle strength, flexibility and balance. The guidelines suggest that aerobic activity should be of vigorous or moderate intensity, muscle strengthening and flexibility exercises should involve the major muscle groups, and that balance training exercises should also be added. Specific recommendations regarding intensity and frequency of exercise have also been mentioned in this guideline.

Since the progressive nature of PD leads to impaired motor activity, the maintenance of normal muscle tone and function becomes a necessity for individuals affected by the disease (Crizzle & Newhouse, 2006). Even though PD medication partially controls the motor symptoms, it has been suggested that adding daily exercise and activity will enhance their beneficial effects. Besides, exercise has been shown to

prevent some of the secondary long term complications of PD, such as joint stiffness. Also, various exercise programs, designed to improve coordination, sway balance, transfer and gait have been proposed in the literature; rhythmic visual or auditory cueing seem quite effective as well (Pelissier & Perennou, 2000).

A regular exercise program should consist of stretching movements, which are critical to hinder the effects of muscle rigidity and achieve a full range of motion. Stretching also improves joint mobility, posture, and circulation, and also releases tension associated with stress. Besides, patients with PD should perform strengthening exercises, since stronger muscles will help avoid joint pain and maintain an erect posture. Increased muscle strength in the arms and legs will improve the ability to get out of a chair and ambulate better. Strengthening exercises could also exert potential training-induced alterations in the neuromuscular system (Falvo, Schilling, & Earhart, 2008). Aerobic conditioning exercises such as walking, swimming, water exercise, and biking have also been shown to benefit individuals with PD by strengthening the heart and lungs, improving stamina and endurance, reducing stress, controlling high blood pressure and high cholesterol, and elevating mood and combating depression (Mehrholz, 2010).

Moreover, endurance exercise has a beneficial effect on reactivity and movement behavior in PD patients following cued application of levadopa. The mechanism underlying these benefits could be the enhanced synthesis and release of dopamine and other cathecolamines in the prefrontal cortex (PFC), the nucleus accumbens, and the basal ganglia. Minor modifications of cathecolamine modulation in the PFC cells, can trigger improved behavior guidance performed by PFC (Muller & Muhlack, 2010).

A randomized control trial experiment exposed PD patients to a high-intensity exercise intervention, using body weight-supported treadmill, and after 24 exercise sessions over 8 weeks, the participants showed post-exercise increases in gait speed, step and stride length, and hip and ankle joint excursion during self-selected and fast gait, and improved weight distribution during sit-to-stand tasks (Fisher et al., 2008). They were compared to a group that performed low-intensity exercises, and the results indicated that high-dose and high-intensity exercises are preferred to the low- dose and intensity ones.

Another eight-week intervention program was conducted by J. Alberts and his colleagues (Alberts et al., 2011). They have compared the effects of forced and voluntary pedaling a bike, and their results supported the same idea: that the high-intensity exercise performed forcefully on a tandem bike improves motor function in people suffering of PD, suggesting that forced exercise may enhance central motor processing and control functions of the basal ganglia.

Thus, the studies conducted so far provide support for the benefits of exercise in mitigating the cardinal motor signs in PD. Future research should focus on identifying the type, dose, and intensity of exercise with the most protective effect on people suffering of PD.

Cognitive Function in PD

The non-motor symptoms (NMS) of PD have been intensely analyzed since the specialists have discovered that PD is not just a ~~–s~~haking palsy", but it actually affects people's senses and intellects as well. The spectrum of non-motor behaviors altered by PD is very extensive and includes anxiety, depression, compulsions, cognitive decline,

sleep disturbances, and autonomic nervous system dysfunction, characteristics that affect patient's function and quality of life.

In the latest years, a growing interest has been shown for the cognitive dysfunction in PD. It has been suggested that individuals with PD suffer from selective cognitive impairments, such as difficulties with attention, concentration, problem solving, set-shifting, and memory, issues believed to be indicative of dysfunction in cortical circuits sub-serving frontal brain regions (Bassett, 2005). Besides, it is believed that almost 30% of PD patients suffer changes in executive function, which are skills that involve planning and execution of daily activities, such as task initiation, attention, abstraction ability, concentration, flexibility, planning, and selectivity of stimuli, self-control, mental control, working memory, and impulse inhibition. PD patients in this category do not fulfill the criteria for dementia, but their performances on particular cognitive tasks are worse than expected given the age and education norms (Pagonabarraga & Kulisevsky, 2012) It is considered that cognitive impairment increases as disease severity increases (Muslimovic, 2005; Riedel, 2010; Verbaan et al., 2007), and that later age at disease onset also contributes to poorer cognitive performance. Non-demented PD patients suffer from visio-spatial deficits, such as poor visual organization and visual construction. The early cross-sectional studies of cognitive performance between people with and without PD reveal that people suffering of PD have a poorer performance on: 1) short term memory tasks; 2) spatial working memory tasks; 3) motor initiation and motor execution times while performing a series of computer generated tasks; and 4) attention set-shifting. Besides, people with PD also spend more time planning their movements and responses.

The term –dysexecutive" syndrome is often applied to PD, because the most prominent cognitive deficit in PD appears in the executive function (Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008). The cognitive impairment in PD is particularly characterized by complications in avoiding non-relevant stimuli or processes during cognition. Also, PD patients have difficulties in free recall, even though they do not present impaired recognition, learning, and long-term retention. This indicates that the memory storage is intact, but the retrieval processes are somehow diminished.

An important aspect that needs to be outlined is whether or not the cognitive impairments are linked to the motor deficits in Parkinson's disease. According to Cooper et al. (1991), the cognitive dysfunction is not related to the frontostriatal dopamine deficiency, a structure responsible for the motor disability, but relies mostly on extrastriatal dopamine system and non-dopaminergic pathology. Besides, Owen et al. (1992) indicated that non-medicated PD patients perform better on cognitive tests than medicated individuals, which leads to the suggestion that levadopa and other PD medication might be responsible for the cognitive impairments. Nonetheless, Cools et al. (2001) suggested that dopaminergic medication has positive or negative impact on the cognitive function, depending on the type of assessment and on the cortico-striatal substructures activated while performing a specific task. An effective approach often used in PD patients with declining cognitive impairment could be the elimination of drugs that accentuate the cognitive deterioration. Cools and his colleagues (Cools et al., 2001) suggested that medication can benefit aspects of cognitive function that rely on circuitry connecting the dorsolateral prefrontal cortex and the posterior parietal cortex to the dorsal caudate nucleus. Sometimes, the cost of improved mentation is high, and

consists of worsening the motor function, thus a well-balanced strategy is required for effectively managing both the cognitive and motor function of PD patients.

Early identification of Mild Cognitive Impairment (MCI) in people with PD could serve as a potential predictor of dementia in PD (Marder, Tang, Cote, Stern, & Mayeux, 1995), and could assist in the application of different pharmacological and non-pharmacological therapies. Patients with MCI present a higher risk of developing dementia, and thus future intervention strategies should focus on delaying or preventing forthcoming cognitive decline.

Exercise and Cognitive Function in PD

Until recently, treatment of cognitive dysfunction in PD was based primarily on patient and family education, behavioral interventions, and the use of cholinesterase inhibitors (Bassett, 2005). For many years, little attention was given to the effects of exercise on the cognitive function in people with PD, particularly because of the lack of evidence and measurable results in this non-pharmacological approach. At the present time, benefic effects of exercise on cognitive function have been demonstrated in animal models, and also in a large number of clinical studies for younger and older adults, as well as for individuals with PD (J. Ahlskog, 2011; K. Cruise et al., 2011; Erickson & Kramer, 2009; Kramer et al., 2006; Murray, Sacheli, Eng, & Stoessl, 2014; A. Ridgel, C.-H. Kim, E. Fickes, M. Muller, & J. Alberts, 2011; Phillip D. Tomporowski, Lambourne, & Okumura, 2011). The cognitive-related benefits in animals include favorable influence on neuronal survivability and function, neuroinflamation, and neuroendocrine response to stress (Baker et al., 2010). Physiological processes, such as glucoregulation and cardiovascular health are also positively influenced by exercise. When these functions are

impaired, the risk of developing cognitive impairment and neurodegenarative diseases is greatly increased (Baker et al., 2010).

The results of clinical studies performed so far, give encouraging evidences for exercise-induced brain repair, neuroprotection, or reorganization neuroplasticity and behavioral recovery, both in animal models with PD. (M. A. Hirsch & Farley, 2009) and in older adults (Erickson & Kramer, 2009).

In PD, the mechanisms underlying neuroprotection could be due to the release of neurotrophic factors, and greater cerebral oxygenation, which together promote new cell growth and cell survival (M. A. Hirsch & Farley, 2009). It has been found that exercise stimulates dopamine synthesis in remaining dopaminergic cells and thus reducing symptoms. Specialists suggest there are five key principles of exercise that enhance neuroplasticity in relation to PD, these being: (a) intensive activity maximizes synaptic plasticity; (b) complex activities promote greater structural adaptation; (c) activities that are rewarding increase dopamine levels and therefore promote learning/relearning; (d) dopaminergic neurons are highly responsive to exercise and inactivity (~~–u~~se it or lose it"); (e) where exercise is introduced at an early stage of the disease, progression can be slowed.

From these key principles some general conclusions can be drawn. First, any exercise is better than no exercise at all, patients being encouraged to choose a type of exercise that they enjoy doing, and will perform with regularity. Second, the earlier an exercise intervention program is applied to patients, the slower the progression of the disease will be. Besides, maximum effort will exhibit maximum benefits, thus moderate to high-intensity exercises being more beneficial for synaptic plasticity than low-intensity

activities (Ridgel, Vitek, & Alberts, 2009). Also, multi-tasking actions are known to create a higher rate of neuron firing leading to positive neural adaptations, and promoting neuroplasticity. And finally, activities that are rewarding in nature, such as those who display immediate positive effects have been shown to increase the dopamine levels, and thus promoting learning/relearning. Exercise could be rewarding in the sense that it helps individuals sleep better, improve mobility, strength and balance, have an increased self-esteem, be in a better mood, increase appetite, to name just a few.

Regarding the types of exercise with the most promise for mitigating favorable cognitive changes in people with PD, Jay L. Alberts (2011) suggests that there is not enough data at this time to recommend one specific exercise over another. Some studies support the idea that moderate to high-intensity aerobic exercise could potentially exert favorable effects on the executive function since it triggers plasticity related changes in the central nervous system, such as synaptogenesis, enhanced glucose utilization, angiogenesis and neurogenesis (Baker et al., 2010; Erickson & Kramer, 2009; M. A. Hirsch & Farley, 2009). In older people with intact cognitive function, aerobic exercise has been shown to reduce inflammation, suppress oxidative stress and stabilize calcium homeostasis (Cotman, 2007). The release of brain-derived-neurotrophin (BDNF), glia-derived-neurotrophin (GDNF), nerve growth factor (NGF) and galanin while performing aerobic exercise it is considered to exert positive effects on synaptic plasticity, enhanced cognitive ability, learning and memory (Colcombe & Kramer, 2003). However, most of these encouraging effects come from studies of brain injury related to stroke and spinal cord injury, and from animal models of PD. Caution is necessary in extrapolating to humans the positive results of well-controlled trials using laboratory animals.

Working memory in PD

Working memory (WM) plays a fundamental role in human's complex cognition. It is a theoretical construct that refers to the mechanisms underlying the maintenance of task-relevant information during the performance of a cognitive task (A. D. Baddeley & Hitch, 1974; Just & Carpenter, 1992). Working memory is considered to be a central construct in cognitive psychology and, more recently, in cognitive neuroscience and it is thought of as being ~~"p~~erhaps the most significant achievement of human mental evolution" (Goldman-Rakic, 1996).

The hallmark of WM is the ability to both maintain information in a transient short-term store of limited capacity and simultaneously manipulate and transform information. In motor behavior, working memory plays an important role in information processing and specifically in response-selection stage. In response-programing stage, working memory is responsible for retrieving information from long-term memory (LTM) in the form of stored motor programs, or other well-learned information about a task. In WM, information from short-term-sensory store (location of seen objects, speed of flying ball) can be integrated with information from LTM, creating an ~~"a~~ction plan". The prepared movements are then triggered from working memory to generate muscle contraction and actions.

The development of the construct of working memory was particularly important to theory development in cognitive aging, as it provided a way to measure the construct of processing resource and to determine whether age-related shrinkage in working memory capacity was the basis for decreased age related performance on a range of cognitive tasks.

According to Beato et al. (2008), alteration of working memory could be partly responsible for the executive function impairments encountered in people with PD. Also, Fournet and his colleagues (2000) tried to determine if cognitive impairments in PD could be explained by a central executive (CE) deficit in Baddeley (1986) WM model. Their findings suggest that PD patients are significantly impaired in WM tasks, with no differences in verbal or spatial parameters and that withdrawal of dopaminergic medication affects WM performance but only on double span task, suggesting that the CE component is sensitive to dopaminergic medication. As for the effects of exercise on the executive function it is believed that acute passive cycling improves set-shifting in people with PD, but future studies should focus on additional measures of executive function, such as working memory, set-activation, and maintenance (Ridgel et al., 2011).

CHAPTER 3

THE EFFECTS OF EXERCISE ON EXECUTIVE FUNCTION IN INDIVIDUALS WITH PARKINSON'S DISEASE

Caciula, M. C., Horvat, M., Tomporowski, P. D. To be submitted to *Movement Disorders Journal.*

Abstract

Introduction. Parkinson's disease (PD) is characterized by progressive loss of motor function, followed by behavioral, physiological, and cognitive modifications in a great proportion of patients. Cognitive function impairments are observed relatively early after the onset of PD and if not treated accordingly, can progress to dementia. Exercise is considered a valuable tool in improving or delaying the progression of motor and cognitive aspects of the disease. However, the optimal delivery content of exercise for people with PD has not been identified yet. The purpose of this study was to identify the effects of different frequencies of exercise on selective aspects of executive function, such as working memory (WM) and cognitive flexibility (shifting) in individuals with PD. **Methods.** Forty-three participants (M_{age} = 68.5 (SD = 11.3), 26 males), with idiopathic PD stages 2 - 3 (Hoehn & Yahr scale) completed two cognitive tasks (Auditory Switch Task and *N*-back task), at baseline, and after 12 weeks of multimodal exercise training. Global switch costs (ms) and response accuracy (% correct responses) were calculated for the switch task, and response time (RT) (ms), and accuracy (% correct responses) for the *N*-back task. The participants were divided into two training frequency groups: a) a high – frequency: 4 – 5 times each week (N = 23, M_{age} = 68.6 (SD = 5.8), 16 males), and b) a low – frequency: 3 times or less each week (N = 20, M_{age} = 67.6 (SD = 4.5), 10 males). **Results**. Although both frequency groups improved global switch costs and *N*-back RT, the high - frequency group displayed greater gains than the low - frequency group. Mixed factorial ANOVA revealed a significant interaction between time and exercise – frequency for global switch costs (F (1, 41) = 5.53, $p < .05$., $\eta_p^2 = 0.09$), and N-back RT (F (1, 41) = 14.96, $p < .001$, $\eta_p^2 = 0.26$), and significant main effects of time for global switch costs accuracy (F (1, 41) = 5.08, $p <$

.05, $\eta_p^2 = 0.11$), and *N* – back accuracy (*F* (1, 41 = 17.37, *p* < .001, $\eta_p^2 = 0.29$). **Discussion.** The results of the study suggest that high frequency of multimodal exercise is beneficial for WM and cognitive flexibility in individuals with PD and could be an important component in preserving executive functioning in this population.

Key words: Parkinson's disease, exercise frequency, working memory, cognitive flexibility.

Introduction.

Parkinson's disease (PD) is primarily perceived as a motor disorder and is characterized by a progressive neurodegeneration of the basal ganglia which affects the motor control of planned and unplanned movements (Rosenbaum, 2006). Other characteristic of this disorder are the cognitive impairment and dementia that have been increasingly more recognized as associated features of PD. In this context, depression and indices of executive function, especially working memory (WM), are among the risk factors for the progression of dementia in PD (PD-D) (Marder, Tang, Cote, Stern, & Mayeux, 1995; Stern, Marder, Tang, & Mayeux, 1993; Woods & Troster, 2003). Cognitive impairment is particularly evident by complications in avoiding non - relevant stimuli or processes during cognition. Also, patients with PD have difficulties in free recall, even though they may not present impaired recognition, learning, and long-term retention. This indicates that memory storage is intact, but the retrieval processes are somehow diminished (Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991).

Some early and central features of dementia in individuals with PD are fluctuating attention, slower response times and vigilance (Miller, Price, Okun, Montijo, & Bowers, 2009; Verbaan et al., 2007). Other indicators of the impaired executive function may include poor performance in tasks involving planning, problem solving, set-elaboration, set shifting, and set maintenance (Pagonabarraga & Kulisevsky, 2012). Also, dual – tasking studies revealed exacerbated gait impairment and postural control while performing a concurrent cognitive task (Holmes, Jenkins, Johnson, Adams, & Spaulding, 2010; Kelly, Eusterbrock, & Shumway-Cook, 2012). As for the memory functions, it is apparent that prominent WM, explicit, and implicit memory deficits can be found early in

the course of the disease (Muller, Wachter, Barthel, Reuter, & von Cramon, 2000; Owen et al., 1992; Zgaljardic et al., 2007).

Conceptually, working memory is a dynamic cognitive system required for the concurrent storage and processing of information (Baddeley, 1992; Just & Carpenter, 1992). The hallmark of WM is the ability to both maintain information in a transient short-term store of limited capacity and simultaneously manipulate and transform information. The development of the construct of working memory is particularly important to theory development in cognitive aging, and provides a way to measure the construct of processing resource and to determine whether aging and structural changes in the brain are the basis for decreased age - related performance on a range of cognitive tasks (Hale et al., 2011).

Alteration of working memory could be partly responsible for the executive function impairments encountered in individuals with PD (Beato et al., 2008). Fournet and his colleagues (2000) tried to determine if cognitive impairments in PD could be explained by a central executive (CE) deficit in Baddeley's (1992) WM model. Their findings suggest that PD patients are significantly impaired in WM tasks, with no differences in verbal or spatial parameters and that withdrawal of dopaminergic medication affects WM performance but only on double span task, suggesting that the CE component is sensitive to dopaminergic medication. As the disease progresses WM tends to deteriorate in people with PD, and to interfere with their mobility and activities of daily living by lowering their psychomotor speed (Koerts, Van Beilen, Tucha, Leenders, & Brouwer, 2011).

Until recently, treatment of cognitive dysfunction in PD was based primarily on patient and family education, behavioral interventions, and the use of cholinesterase inhibitors (Bassett, 2005). Multiple controlled trials and clinical studies have looked at the effects of medication and of deep brain stimulation (DBS) on selective aspects of cognitive function in individuals with PD. Apparently dopaminergic medication improves or impairs cognitive performance depending on the nature of the task and the basal level of dopamine function in underlying cortico-striatal circuitry (Cools, Barker, Sahakian, & Robbins, 2001). As for the DBS approach, evidence suggest that certain aspects of cognitive performance may decline after the surgery, especially when the therapeutic target is the subthalamic nucleus.

For many years, little attention was given to the effects of exercise on the cognitive function in people with PD, particularly because of the lack of evidence and measurable results in this non-pharmacological approach. At the present time, the benefits of exercise on cognitive function have been demonstrated in animal models, as well as for individuals with PD (J. Ahlskog, 2011; Cruise et al., 2011; Murray, Sacheli, Eng, & Stoessl, 2014; Nocera, Altmann, Sapienza, Okun, & Hass, 2010; Ridgel, Kim, Fickes, Muller, & Alberts, 2011). The cognitive-related benefits in animals include favorable influence on neuronal survivability and function, neuroinflamation, and neuroendocrine response to stress (Baker et al., 2010), while in people with PD vigorous exercise is thought to have a neoroprotective effect (J. Ahlskog, 2011). The mechanisms underlying neuroprotection could be due to the release of neurotrophic factors, and greater cerebral oxygenation, which together promote new cell growth and cell survival (Hirsch & Farley, 2009). It has been demonstrated that exercise stimulates dopamine

synthesis in remaining dopaminergic cells and thus reducing symptoms (Tajiri et al., 2010). More results suggested that exercise might selectively benefit cognitive functioning in people with PD, by improving frontal lobe based executive function (Cruise et al., 2011). Studies also indicated that exercising three or more times per week may improve higher – order cognitive function, and delay the onset of dementia in people with neurodegenerative disease (Larson et al., 2006).

Although the latest findings regarding the benefits of exercise for cognitive function in individuals with PD are promising, there is still a lack of information regarding the optimal frequency of exercise training for cognitive benefits in this population. The present study was conducted with the purpose to identify the effects of different frequencies of multimodal exercise on selective aspects of executive function in individuals with idiopathic PD without dementia. We expected to see changes of executive functioning in individuals with PD following exercise intervention, with the high – frequency group displaying greater improvements than the low – frequency group. These modifications were anticipated based on motor learning theories which state that through practice and learning of new movements and skills, individuals become more cognitively engaged due to new cell growth and neuroplasticity (Petzinger et al., 2013).

Method.

Participants. A total of forty-three individuals (n = 43; 26 males and 17 females) diagnosed with idiopathic PD (stages II-III according to the modified Hoehn-Yahr scale) from the Atlanta Metropolitan Area participated in this study. All participants were recruited from Atlanta Metropolitan area through the PD Support Group meetings, the PD exercise classes organized under the auspice of American Parkinson's Disease

Association (APDA) the Georgia Chapter, and also through the monthly educational meetings from Atlanta. Table 3.1. summarizes the basic demographic and clinical characteristics of the participants. Individuals were included in this study based on the following criteria: 1) a Montreal Cognitive Assessment (MoCA) scores ≥ 22 (a score lower than 21 indicates increased odds of dementia) (Nasreddine et al., 2005); 2) age between 50 yr. and 80 yr. and 3) participants did not present other health related problems that could interfere with safe participation in an exercise training program (e.g. they have been cleared by their physician). Participants were excluded from the study if they were experiencing any neurological (other than PD), or motoric impairments that might impact their mobility, and if they were suffering from a cardiovascular disease or other metabolic disorders. Also, participants were excluded from the study if they had undergone deep brain stimulation surgery. Participants were grouped into one of two exercise-frequency groups: a high – frequency group (n = 23; exercise 4-5 times/ week, for 30 – 45 min. /bout), and a low – frequency exercise group (n=20; exercise dose ≤ 3 times/ week, 30 – 45 min. /bout).

Procedures. All participants were required to read and sign the University of Georgia Institutional Review Board (IRB) consent forms prior to beginning any testing and exercising. All participants completed two testing sessions scheduled one week apart prior to the exercise intervention, and one testing session at the conclusion of 12 weeks of exercise training. The effects of medication on PD participants were controlled by assessing and exercising the participants at 2 hours after medicine ingestion, which is the approximate peak of the medication effect (Ouchi, 2001). During the first session, the participants read and signed informed consent, completed a demographic and medical

history questionnaire, took a screening test (Montreal Cognitive Assessment), and were trained to perform the Auditory Switch Task and the *N*-back task.

Session two took place one week later and had three phases. First, all participants received retraining for both within- and between Switch Task category (60 trials each), and for each of the *N*-back (0-, 1-, 2-, 3 – back) conditions (25 trials each). Second, all participants were asked to complete a series of three Switch tests, which differed in the type of discrimination required and the number of stimuli presented. Two test types required within-category decisions (pure conditions): 200 number presentation (even/odd discrimination) and 200 letter presentation (consonant/vowel discrimination). One test type required alternating-category decisions (mixed condition) made of 220 numbers and letters. Third, for the N-back task, the participants completed 12 blocks of trials (three blocks of each of the four conditions) with each block consisting of 25 trials.

At the end of the 12 weeks of multimodal exercise intervention, all participants completed a systematic replication of session 2, performed with alternate forms of the switch task and the *N*- back. All training and testing trials were administered by the student investigator in a quiet room, sitting in front of a laptop, wearing headphones and pressing on a regular size optical mouse. A detailed description of the screening and testing instruments is presented in the section below.

Screening Instrument.

Montreal Cognitive Assessment (MoCA). The Montreal Cognitive Assessment (MoCA) was created in 1996 by Dr. Ziad Nasreddine in Montreal, Canada. It was validated for assessing in the setting of individuals with mild cognitive impairment, and has subsequently been adopted for use clinically with other populations

with cognitive deficits. The MoCA test was preferred to the Mini-Mental State Examination (MMSE) because MoCA test may be a more sensitive tool to identify early cognitive impairment in people with PD (Zadikoff et al., 2008). The MoCA test is a one-page 30-point test administered in approximately 10 minutes. A final total score of 26 and above indicates no impairment, and a score lower than 26 indicating mild cognitive impairment. The MoCA assesses several cognitive domains. The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately 5 min. Visio-spatial abilities were assessed by asking the participant to draw a clock and set a pre-specified time (3 points) and to copy a three-dimensional cube (1 point). Multiple aspects of executive functions are assessed using an alternation task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points). Attention, concentration and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a verbal serial subtraction task (3 points), and verbally counting listing digits forward and backward (1 point each). Language was assessed using a three-item naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task. Finally, the participant's orientation to the current time and place is evaluated (6 points).

Cognitive Function Assessments.

Auditory Switch Test. The first cognitive task was an auditory switch test designed to measure cognitive flexibility, a very important aspect of executive function (Miyake et al., 2000) In this assessment computer-generated letters or numbers were presented binaurally to a headphone via a commercial software program ("Cedrus.

SuperLab.,"). The letters consisted of four vowels (A, E, I, and O) and four randomly selected consonants (B, D, L, and C). The numbers consisted four even numbers (2, 4, 6. and 8) and four odd numbers (1, 3, 5, and 7). The participant was required to respond to each stimulus by pressing the appropriate key on a regular size optical mouse (even number-left key; odd number-right key; vowel letter-left key; consonant letter-right key). Each key press was followed 100 ms later by the presentation of the next stimulus. Two types of stimulus blocks of trials were used: in homogenous blocks, participants have been asked to respond to letters only or numbers only; in mixed or heterogeneous blocks, participants had to respond alternatively to letters and numbers. In mixed blocks, letters or numbers have been presented in series lengths of two, three or four stimuli. The letter-number category discrimination was switched following each series. In each block of trials, the initial 4 trials were considered practice and not evaluated. In the remaining we alternated between non-switch trials (i.e., repetitive within-category discriminations) and switch trials (i.e., a change in category discrimination), with an equal number of switches to even-odd and vowel-consonant conditions. Response times (RT) and response accuracy (% correct responses) were recorded for each trial.

After the training sessions, each participant performed a series of three tests, which were different in the type of discrimination required and in the number of stimuli. Two tests required within-category decision (pure condition): number presentation (even/odd discrimination) or letter presentation (vowel/consonant discrimination). One test type required alternating-category decisions (mixed condition) composed of both letters and numbers. All participants completed one 200 numbers-only test, one 200 letters-only test, and one 220 mixed-condition test. They performed the tests while seated in a quiet room and were instructed to respond as quickly and accurately as possible.

Another series of tests with the same protocol was administered to the participant after the twelve weeks of exercise training. This is a protocol similar to the one used by Okumura, Cooper, Ferrara, and Tomporowski (2013).

***N*-back task**. The *n*-back task is a continuous performance task that is commonly used in cognitive neuroscience to measure verbal and visual working memory. Participants performed the *n*-back task following the same protocol as the one used by Perlstein and his colleagues (2003). They used the index and middle fingers of their dominant hand to press one of two buttons denoting ―target" and ―non-target" using the same optical mouse. In the 0-back condition, the target was any letter that matched a pre-specified letter (i.e., ―e"). Thus, this condition required sustained attention but no working memory demand. In the 1-back condition, the target was any letter identical to the letter immediately preceding it (i.e., the letter presented one trial back). In the 2-back condition, the target was any letter that was identical to the one presented two trials back. In the 3-back condition, the target was any letter that was identical to the one presented three trials back. Stimuli were random consonants presented binaurally to the headphones via the same commercial software program ("Cedrus. SuperLab.,") for a 500-ms duration with a 2500-ms inter-stimulus interval. Participants completed 12 blocks of trials (three blocks of each of the four conditions) with each block consisting of 25 trials. The first three trials of each block were never targets and of the remaining trials 30% were targets. A short break (5–20 s) between blocks was provided to allow participants to rest. Prior to the start of the actual task, participants were trained on each of the four conditions. Participants were given up to three practice blocks (of 25 trials each) per condition with feedback on their performance, until they demonstrated that they understood the task and their performance stabilized. Another set of tasks with a similar design was performed by

the participants after the exercise training. Response time (RT) and accuracy measures were obtained for each trial.

The *n*-back task captures the performance of the active part of working memory. When *n* equals 2 or more, it is not enough to simply keep a representation of recently presented items in mind; the working memory buffer needs also to be updated continuously to keep track of what the current stimulus must be compared to. To accomplish this task, the subjects need to both maintain and manipulate information in working memory (Miller et al., 2009).

Exercise protocol. The exercise protocol documentation was based on daily calendars recorded by all participants with the type, duration and perceived intensity of each activity. All subjects engaged in group exercise classes organized under the auspice of American Parkinson's Disease Association (APDA). The activity was consistent throughout all five senior centers located in Sandy Springs, Decatur, Roswell, Atlanta and Douglasville. The group exercise classes were conducted and recommended by two males and three females instructors certified by APDA and included aerobic activities such as: walking, running, stationary bike, water aerobics, water volleyball; resistance exercises with bands and dumbbells, and movement activities such as zumba and Tai Chi. Thus, the exercise intervention was mainly goal – oriented and focused on aspects of physical function specific to people with PD. The mean duration of the sessions was 42 minutes (±7 min.). The weekly amount of exercise that a participant reported was the criterion for classifying individuals into either the high – frequency group (4 - 5 times/ week), or the low - frequency group (≤ 3 times/ week). The dominant perceived intensity reported by participants in this study was moderate to heavy.

Statistical Analyses.

Auditory Switch Task. Separate switch cost scores were calculated for tests composed of 200 and 220 trials. Global switch cost scores were calculated as recommended by Wasylyshyn et al. (2011). The average RT of the two pure, within-category conditions (number and letter discrimination) was subtracted from the average RT of switch and non-switch trials in the mixed, between-category condition. The frequency of the correct responses made during the mixed, between-category tests of 220 trials was converted to percentage of total responses. The global switch cost scores and accuracy scores are presented in Table 3. For both the global switch cost scores and percentage accuracy scores an initial 2 (exercise frequency group: high-frequency, low-frequency) x 2 (time: pre-exercise, post-exercise) mixed measures factorial ANOVA, with time as the repeated factor was conducted to assess the effects of exercise frequency and training. Analyses were conducted using SPSS 22 software ("SPSS IBM, New York, U. S. A.,"). The $p = 0.05$ rejection level was used in all analyses.

N-back. For each participant, means and standard errors of RTs for correct responses were computed for each n-back condition. Extreme RTs (defined as greater or less than three standard deviations, calculated per participant, per condition) were excluded from further analyses. Excluded trials accounted for only 2.4% of the total number of trials, and thus it is unlikely that their exclusion would alter the overall pattern of the data. N-back accuracy was calculated with the following algorithm: [1 - ((number of commissions + number of omissions)/total possible correct)] x 100. Mixed measures factorial ANOVA were used to examine group, time, and load differences on these measures. Significant effects were decomposed through post-hoc t-tests. Analyses were

conducted using SPSS 22 software ("SPSS IBM, New York, U. S. A.,"). The $p = 0.05$ rejection level was used in all analyses.

Results.

Auditory Switch Task

Global switch costs. Means and standard errors for the global switch costs pre-exercise and post-exercise are presented in Table 3.2 and in Graph 3.1. A mixed factorial ANOVA of the switch cost scores yielded a significant interaction between time and exercise frequency, F (1, 41) = 5.53, $p < .05$, $\eta_p^2 = 0.09$, indicating a greater improvement in cognitive flexibility for the high – frequency exercise group after the intervention. Post-hoc *t*-tests indicated that the two exercise frequency groups were not significantly different prior to the exercise intervention, t = - 0 .04, $p = 0.96$, but their performance was significantly different after the 12 weeks of training t = - 2.11, $p < .05$.

Response Accuracy means is presented in Table 3.2 and in Graph 3.2. A mixed measures factorial ANOVA revealed a significant main effect of time on the response accuracy, F (1, 41) = 5.08, $p < .05$, $\eta_p^2 = 0.11$, indicating that regardless of the frequency, exercise improves shifting accuracy in individuals with PD. The group by time interaction was non-significant F (1, 41) = 1.64, $p = .2$, $\eta_p^2 = 0.39$.

N-back task

Response time (RT). Means and standard errors of RT are presented in Table 3.3 and in Graph 3.3. A 2 (time) X 4 (cognitive loads) X 2 (exercise frequency groups) mixed-measures factorial ANOVA was conducted, with time and load as the within-subjects factors. Analysis of RTs revealed a significant interaction between time and group, F (1, 41) = 14.96, p < .001, $\eta_p^2 = 0.26$, indicating a greater improvement in

working memory response time for the high – frequency exercise group after the intervention. Post-hoc *t*-tests revealed that regardless of the WM load there was no significant difference between the two groups prior to exercise, and after the exercise intervention. Also, analysis revealed a significant main effect of load, F (3, 123) = 468.94, p < .001, $\eta_p^2 = 0.92$. Post-hoc *t*-tests indicated that RTs for each load differed significantly from RTs for all other loads, both prior to exercise and at the end of the intervention. Overall, there was a tendency of increased RTs as working memory load increased (Table 3).

Response Accuracy (% correct). Means and standard errors of RT are presented in Table 3.3 and in Graph 3.4. A 2 (time) X 4 (cognitive loads) X 2 (exercise frequency groups) mixed-measures factorial ANOVA was conducted, with time and load as the within-subjects factors. Analysis of response accuracy revealed a significant main effect of time, F (1, 41) = 17.37, $p < .001$, $\eta_p^2 = 0.29$, suggesting that both frequency groups improved accuracy in working memory after the exercise intervention. Also, analyses revealed a main effect of load, F (3, 123) = 613.96, $p < .001$, $\eta_p^2 = 0.93$. Post-hoc *t*-tests indicated that accuracy for each load differed significantly from accuracy for all other loads, both prior to exercise and at the end of the intervention. Overall, there was a tendency of decreased accuracy as working memory load increased (Table 3).

Discussion.

The primary purpose of our study was to identify the effects of different frequencies of weekly exercise on selective aspects of executive function (EF) in people with idiopathic PD, after 12 weeks of multimodal exercise training. Our findings suggest

that changes in executive function depend on a specific amount of weekly exercise, with higher frequencies triggering more benefits than lower frequencies.

We examined participants' performance on an Auditory Switch Task and on the *N*-back task before and after the exercise intervention. Through these cognitive tasks we tried to detect changes in two out of the three interrelated components of executive function proposed by Miyake (2000). According to his theory, there are three aspects of EF: updating, inhibition, and shifting. First, updating is defined as the continuous monitoring and quick addition or deletion of contents within one's working memory, and it is assessed in our study thorough the *N*-back task. Second, inhibition is one's capacity to supersede responses that are pre-potent in a given situation, and third, shifting is one's cognitive flexibility to switch between different tasks or mental states, and it is the object of the Auditory Switch Task in the present study.

Analyses of the global switch costs data revealed a statistically significant interaction between time and exercise - frequency. The switch cost index reflects the changes in the attention-demanding mental processes required to abandon one response set and to reconfigure a different response set (Monsell, 2000; Rogers DR, 1995). Our findings suggest that higher frequencies of weekly exercise are beneficial for cognitive flexibility in non-demented people with PD. As for the Switch Task accuracy, analyses of data indicated a non - significant interaction between time and exercise frequency and a significant main effect of time only, suggesting that regardless of the frequency, exercise might have a positive impact on response accuracy. It may also be that the lack of significant change in accuracy could be explained by the ceiling effect, since most participants' responses were between 90% and 100% correct. Speed–accuracy tradeoff between the switch cost scores and response accuracy, which often occurs when

individuals attempt to maintain or reduce RT but at the cost of increasing errors, was non-existent, providing additional support for the benefits of exercise on the shifting aspects of executive function in individuals with PD. Our results are similar to the findings of Tanaka et al. (2009), Ahlskog (2011), and Cruise et al. (2011). Their findings suggest that physical exercise benefits executive function in older individuals with PD, and that vigorous exercise and physical fitness may have a neuroprotective effect in PD. The changes in cognition could be due to enhanced neuroplasticity, exercise-related protection from dopaminergic neurotoxins, and increased neurotrophic factor expression (J. E. Ahlskog, 2011). In addition, Benjamin and his colleagues' findings (2007) suggest that people with generally lower cognitive performances tend to benefit more from exercise interventions, and this might be the case of our participants since their MoCA screening scores indicated a mild impairment of their cognition. Another notable finding was Kramer's (1999) selective cognitive improvement hypothesis, which states that aerobic exercise, as opposed to anaerobic exercise (stretching and toning) leads to selective, rather than generalized, cognitive benefits.

The within-subjects analysis of the *N*-back RTs indicated a significant interaction between time and exercise frequency but no interaction between load and exercise - frequency, since there was a common pattern of increased RTs as working memory load increased. The response accuracy data analyses indicated no significant interaction between loads, exercise dose, and time, but a simple main effect of time, and load separately. Thus participants have improved response accuracy following exercise, but maintained the common pattern of reduced accuracy as the WM load increased. The between-subject analyses revealed no significant effect of exercise - frequency on participants' response accuracy. These results suggest that exercise could benefit aspects

of WM in non-demented people with PD, with higher frequencies of exercise training exerting more benefits on people's RT than lower frequencies, and exercise, regardless of the amount, improving aspects of response accuracy. Again, there was no speed-accuracy tradeoff for the *N*-back task, which might be another argument to support the potential benefits of multimodal exercise on selective aspects of executive functions.

These results are consistent with evidence from animal models that supports the role of exercise to promote neuronal proliferation, neoruprotection, and neurogenesis in the basal ganglia related to cognition (B. Fisher et al., 2004; B. E. Fisher et al., 2008). Also, previous clinical studies showed that various types of exercise, and more specifically, exercise that incorporates goal-based training and aerobic activity have the potential to improve both cognitive and automatic components of motor control in individuals with mild to moderate disease through experience-dependent neuroplasticity (J. Ahlskog, 2011; Petzinger et al., 2013; Tanaka, 2009). In this study, all participants have been exposed to group exercise classes specifically designed for people with PD, thus the exercise training was goal-based and helped the participants to learn through instructions, feedback (reinforcement), and encouragement to perform beyond self-perceived capability. Through practice and learning of new movements and skills, individuals with PD are thought to become more cognitively engaged, and this might be another potential explanation for the changes observed in selective aspects of executive function following chronic multimodal exercise (Petzinger et al., 2013). Besides, all participants have been consistently exposed to aerobic types of exercise, and it is generally accepted that aerobic exercise promotes brain-derived neurotophic factors (BDNF) release, and greater cerebral oxygenation, which together promote new cell growth and cell survival (Hirsch & Farley, 2009).

Although we have demonstrated the beneficial aspects of cognitive function in PD, this study has limitations such as the lack of randomization, a highly educated sample of participants, which may not represent the typical PD patient, and a small sample size. All participants were tested while on dopaminergic medication, which may have improved task performance given prior findings that dopamine modulates working memory (Costa et al., 2003).

The results of the present study suggest that goal-oriented, multimodal exercises performed consistently, at least four times/ week at moderate to high intensities can benefit selective aspects of executive function, such as WM and shifting, in individuals with PD without dementia. Because of the availability of service in a large metropolitan area, individuals were able to access programs designed specifically for PD. Additionally intervention opportunities such as home – based programs should be encouraged to supplement our findings, while health care providers and policy makers should recommend exercise as part of routine management and neurorehabilitation for PD.

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Table 3.1. Demographic and clinical features of 43 patients with Parkinson's disease.

Variable	HF exercise	LF exercise	p
Number of patients	23	20	
Male/ Female	16/7	10/10	
	mean (SD)	mean (SD)	
Age (years)	68.6 (5.8)	67.65 (4.5)	0.55
Age of PD onset (years)	57.5 (12.9)	58 (13.5)	0.62
PD duration (years)	10.6 (5.2)	9.8 (4.9)	0.83
Hoehn and Yahr	2.3 (0.5)	2.5 (0.4)	0.27
Education (years)	18.3 (2.9)	17.9 (2.7)	0.81
Exercise habits (times/ week)	5.1 (1.1)	2.2 (0.6)	< 0.0001*
MoCA score	25.5 (2.7)	25.4 (2.5)	0.88
UPDRS motor score	26.4 (4.3)	26.5 (5.0)	0.95

HF, high – frequency; LD, low – frequency; SD, standard deviation; MoCA, Montreal Cognitive Assessment; *significant difference ($p < 0.05$); UPDRS, Unified Parkinson's Disease Rating Scale.

Table 3.2. Mean global switch cost scores (ms) (SE), and response accuracy (percent correct) by group and time.

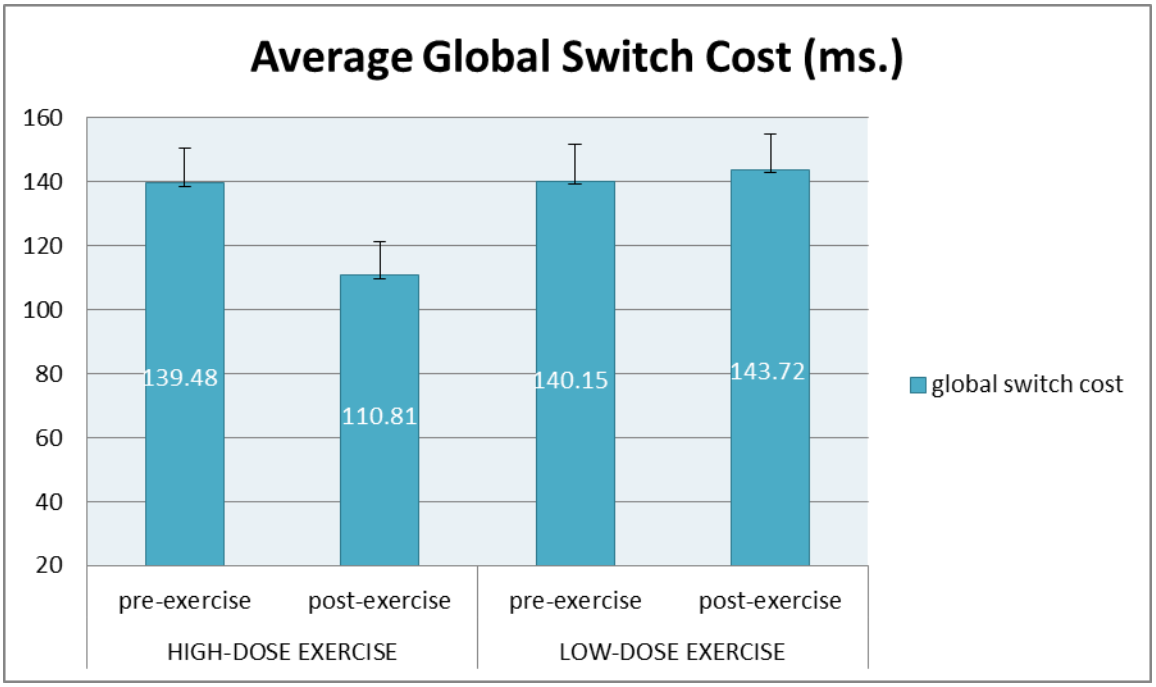
Condition	**High - frequency**	**Low - frequency**
Pre-Exercise		
Switch-cost	139.48 (10.8)	140.15 (11.6)
Accuracy	93.86	94.01
Post-Exercise		
Switch-cost	110.81 (10.6)	143.72 (11.3)
Accuracy	94.93	94.33

Table 3.3. Mean *N*-back RT (ms) (SE), and response accuracy (percentage correct) by group and time.

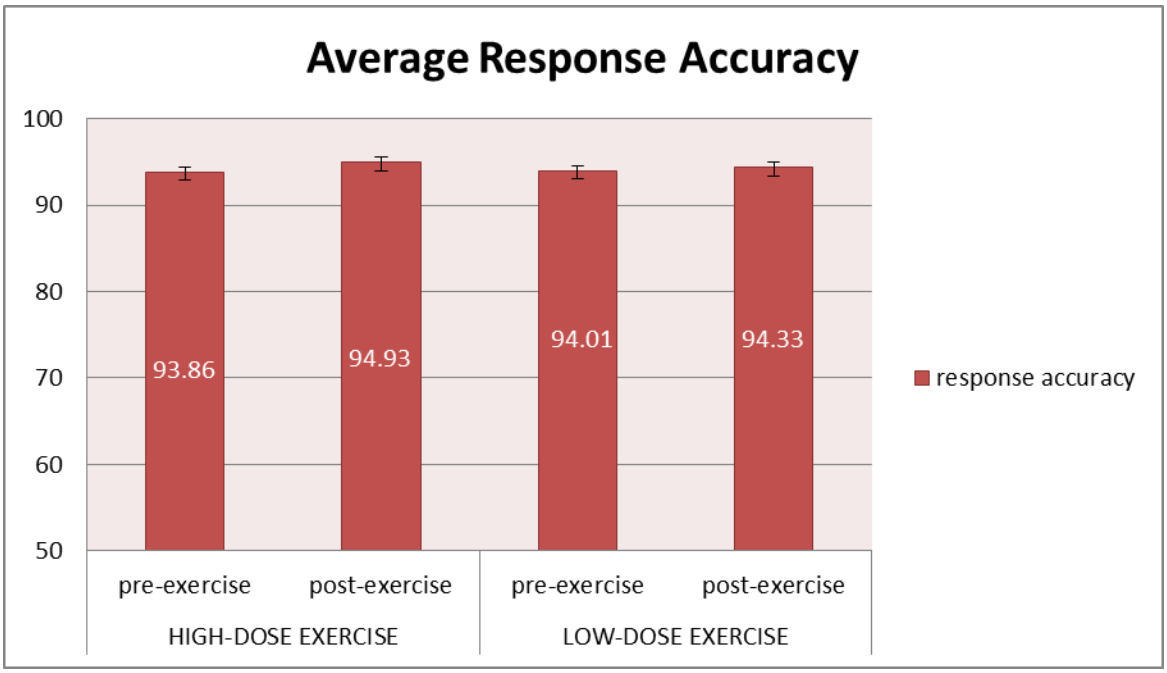
	Group			
	HF - exercise		**LF - exercise**	
	Pre-exercise	Post-Exercise	Pre-Exercise	Post-Exercise
0-back				
Response time	692.02 (23.1)	649.02 (20.04)	700.54 (24.8)	694.62 (21.4)
Accuracy	92.78	94.56	92.05	93.1
1-back				
Response time	789.06 (28.3)	741.43 (24.95)	821.24 (30.41)	806.09 (26.7)
Accuracy	83.08	85.04	83.8	84.05
2-back				
Response time	997.09 (38.8)	954.13 (34.05)	1028.73 (41.6)	1022.67 (36.5)
Accuracy	74.04	76.17	74.25	75.15
3-back				
Response time	1164.16 (40.87)	1083.46 (35.6)	1177.63 (43.8)	1165.1 (38.2)
Accuracy	69.69	71.52	69.05	70.1

HF, high – frequency; LF, low – frequency;

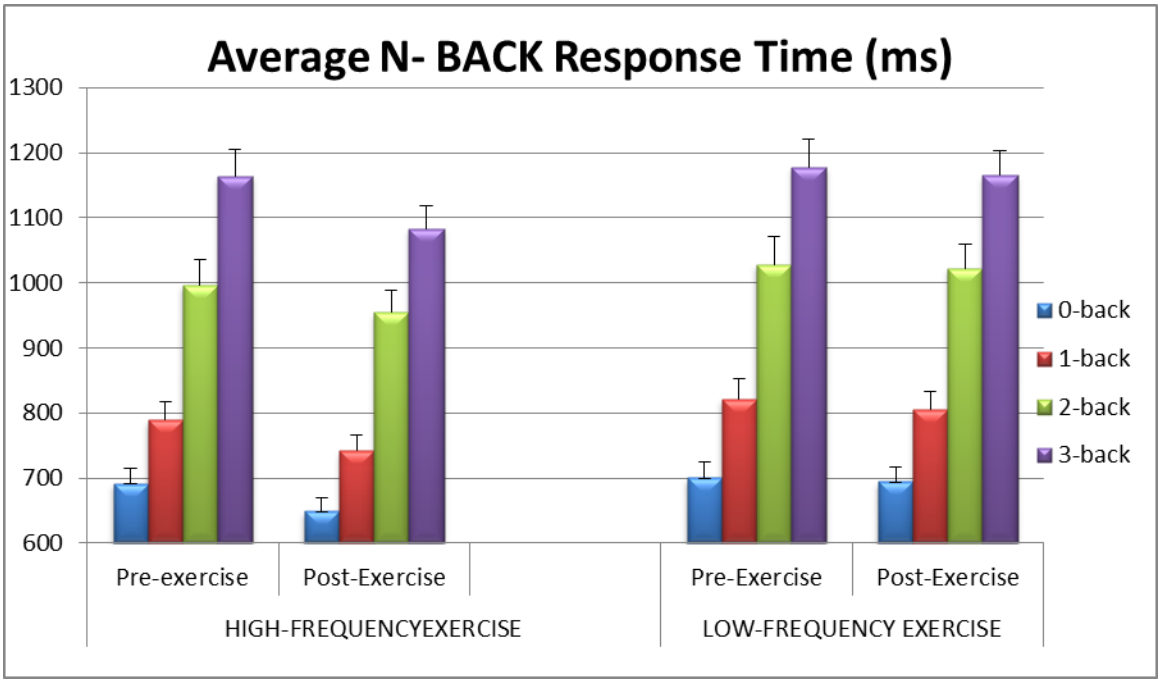
Graph 3.1. Mean global switch cost scores (ms) (SE).



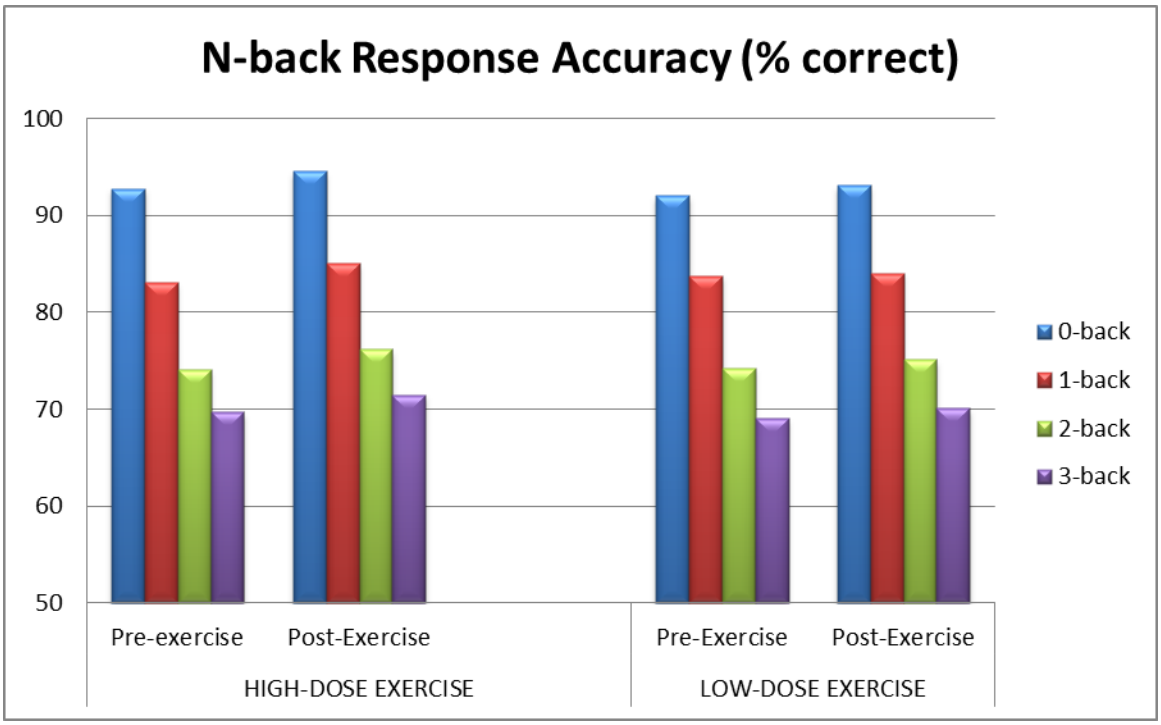
Graph 3.2. Mean response accuracy (percent correct) (SE).



Graph 3.3. Mean *N*-back RT (ms) (SE).



Graph 3.4. Mean response accuracy (percentage correct) (SE).



CHAPTER 4

THE EFFECTS OF EXERCISE ON COGNITIVE FLEXIBILITY AND PHYSICAL FUNCTION IN INDIVIDUALS WITH PARKINSON'S DISEASE

Caciula, M.C., Horvat M., Nocera J.R. To be submitted to *Journal of Parkinsonism and Related Disorders.*

Abstract

Introduction. Parkinson's disease (PD) is characterized by limitations in cognitive and motor function related to the loss of dopamine in the substantia nigra of the midbrain. Individuals with PD experience walking deficits, balance and posture alterations, muscular weakness and deconditioning, as well as progressive cognitive decline. Although the latest findings regarding the benefits of exercise for physical and cognitive function in individuals with PD are promising, there is still a lack of information regarding the optimal frequency of exercise training for cognitive and physical benefits in this population. The purpose of the present study is first, to identify the effects of a high – frequency and a low – frequency exercise intervention program on the physical function in individuals with PD without dementia; and second, to determine the correlation between changes in walking speed and changes in executive function (EF) after 12 weeks of multimodal exercise intervention in this population. **Methods.** Forty-three participants (M_{age} = 68.5 (SD = 11.3), 26 males), with idiopathic PD stages 2 and 3 (Hoehn – Yahr scale) completed the Short Physical Performance Battery (SPPB), and an auditory switch task at baseline, and at the conclusion of 12 weeks of the exercise intervention. Summary performance scores for the SPPB used the summation of the test scores for standing balance, walking speed, and rising from a chair 5 times, while global switch costs and response accuracy were calculated for EF. The participants were classified based on their ability to secure transportation to the exercise program into a high - frequency exercise group (N = 23, M_{age} = 68.6 (SD = 5.8), and a low - frequency exercise group (N = 20, M_{age} = 67.6 (SD = 4.5). **Results**. Based on a mixed factorial ANOVA significant interaction was indicated between time and group, F (1, 41) = 8.37, $p < .05$, $\eta_p^2 = 0.17$ for SPPB summary performance scores, and a significant interaction

between group and task F (2, 82) = 3.65, $p < 0.05$, $\eta_p^2 = 0.08$, for the SPPB scores calculated for each of the three tasks separately. Also, linear regression analysis revealed a significant correlation for differences in walking speed and differences in executive function following 12 weeks of high – frequency exercise, $F(1, 21) = 25.921$, $p < .0005$, and a weak correlation for low – frequency exercise, F (1, 18) = 3.404, p = 0. 082.

Discussion. Based on the data analysis it is apparent that changes in physical function are dependent on the frequency of weekly exercise, and also that differences in walking speed following a high – frequency exercise program could predict changes in executive function in non – demented individuals with PD.

Key words: Parkinson's disease, physical function, cognitive function, exercise frequency.

Introduction.

Parkinson's disease (PD) is a movement disorder caused by an imbalance of chemical messengers in the brain. The primary messenger affected is the neurotransmitter called dopamine, concentrated in the substantia nigra of the midbrain (Stewart A. Factor, 2002). When neurons in the substantia nigra degenerate, the resulting loss of dopamine (DA) causes the nerve cells of the striatum to fire excessively. This makes it difficult to control movements, and is demonstrated by primary motor symptoms associated with PD, including: bradykinesia, postural instability, muscle rigidity, and resting tremor (Rosenbaum, 2006; Sohn, 2003). Symptomatically, the typical feature characterize the onset and progression of PD while functional deficits are the loss of muscle strength, postural stability and balance that effect the basis of motor control and the ability to plan, initiate and execute purposeful movement (Protas et al., 2005).

This is especially evident in the inability to initiate and control gait. Parkinsonian gait is characterized by shuffling steps, a general slowness of movement or total loss of movement (akinesia) in extreme cases (Boonstra, van der Kooij, Munneke, & Bloem, 2008). Functional components in PD demonstrate spatial difficulties such as reduced stride lengths, and temporal components difficulties such as reduced walking speed and increased duration of double support and cadence rate (Hausdorff, Rios, & Edelberg, 2001; Morris, Iansek, Matyas, & Summers, 1998; J. R. Nocera, Horvat, & Ray, 2010). Patients have difficulty initiating a movement, but also demonstrate a reduced ability to stop or change directions (J. R. Nocera et al., 2010). The loss of capabilities due to gait and balance problems are specific to functional decline in quality of life, morbidity, and mortality in patients with PD (Forsaa, Larsen, Wentzel-Larsen, Herlofson,

& Alves, 2008; Muslimovic, Post, Speelman, Schmand, & de Haan, 2008; Pickering, 2007; Rahman, Griffin, Quinn, & Jahanshahi, 2008). The loss of function represent a major threat to ambulatory independence, causing pain, cessation of physical activities, and the onset of cognitive decline.

Cognitive impairment is particularly evident in PD by complications in avoiding non - relevant stimuli or processes during cognition. Also, patients with PD have difficulties in free recall, even though they may not present impaired recognition, learning, and long-term retention. This indicates that memory storage is intact, but the retrieval processes are somehow diminished (Aarsland et al., 2010; Fournet, Moreaud, Roulin, Naegele, & Pellat, 2000). Other indicators of the impaired executive function may include poor performance in tasks involving planning, problem solving, set-elaboration, set shifting, and set maintenance (Pagonabarraga & Kulisevsky, 2012). Also, dual – tasking studies revealed exacerbated gait impairment and postural control while performing a concurrent cognitive task (Holmes, Jenkins, Johnson, Adams, & Spaulding, 2010; Kelly, Eusterbrock, & Shumway-Cook, 2012).

Although PD is a degenerative disease, inactivity may accelerate the progression of symptoms (Tillerson, 2003). Studies have shown that moderate and high levels of physical activity lowers the risk of developing PD (Chen, Zhang, Schwarzschild, Hernán, & Ascherio, 2005), and also suggested that participating with regularity in exercise programs can postpone the onset of the disease (Tsai et al., 2002). A recent cross – sectional study conducted by Ellis and colleagues (2013) identified three major perceived barriers to exercise, including low expectations from exercise, lack of time to exercise, and fear of falling. Recent reviews and research suggest also that exercise is important in

the early stages of PD, and that can have positive effects on both motor and non-motor signs and symptoms of the disease (Lauhoff, Murphy, Doherty, & Horgan, 2013; Murray, Sacheli, Eng, & Stoessl, 2014; Giselle M. Petzinger et al., 2013; van der Kolk & King, 2013)

Different types of exercises were proposed by intervention and randomized controlled trials in order to minimize the negative effects of PD on the motor and functional performance. These studies identified specific exercises to improve mobility (King & Horak, 2009; Nieuwboer et al., 2007; van der Kolk & King, 2013), muscular strength (L. Dibble et al., 2006; L. E. Dibble, Hale, Marcus, Gerber, & LaStayo, 2009), balance (Hirsch, Toole, Maitland, & Rider, 2003), aerobic conditioning (Rodrigues de Paula, Teixeira-Salmela, Coelho de Morais Faria, Rocha de Brito, & Cardoso, 2006), posture (J. Nocera, Horvat, & Ray, 2009) and gait (Nieuwboer et al., 2007).

Other studies have identified an association between walking speed and executive function in healthy older adults, with a decline in walking speed predicting a degeneration of global and executive function (Atkinson et al., 2007; Inzitari et al., 2007; Weuve et al., 2004). Also, exercise improves selective aspects of cognitive function in people with PD (Murray et al., 2014), and more precisely, executive function (EF) which has been increasingly recognized as an associated feature of PD. Walking and mobility are more often linked to EF (Yogev-Seligmann, Hausdorff, & Giladi, 2008), and it is suggested that PD people with poor EF tend to walk slower, have increased gait variability, fall more often, and perform poorly on complex mobility tasks such as rising from a chair and dual tasking (Kelly et al., 2012; Persad, Jones, Ashton-Miller, Alexander, & Giordani, 2008). However, the relationship between gait control and

executive function as a result of exercise intervention programs for people with PD is not documented very well. Based on the loss of cognitive and motor function in PD the purpose of this study was to examine the correlation between walking speed during free ambulation and selective aspects of executive function following twelve weeks of multimodal exercise training, and the effects of exercise on physical function as measured by the Short Physical Performance Battery. We also projected that improvement in ambulation would improve aspects of cognition as measured by and EF task.

Methods.

Participants. Clinical and demographic features of all participants are presented in Table 4.1. A total of forty-three (n = 43; 26 males and 17 females) individuals diagnosed with idiopathic PD without dementia (stages II-III according to the modified Hoehn-Yahr scale). All participants were recruited from Atlanta Metropolitan area through the PD Support Group meetings, the PD exercise classes organized under the auspice of American Parkinson's Disease Association (APDA) the Georgia Chapter, and also through the monthly educational meetings from Atlanta. Individuals with PD have been included in this study based on the following criteria: 1) Montreal Cognive Assessment (MoCA) scores $\geq$ 22 (a score lower than 21 indicates increased odds of dementia) (Nasreddine et al., 2005) 2) age between 50 and 80; 3) participants did not present other health related problems that could interfere with safe participation in an exercise training program (e.g. they were cleared by their physician), and 4) participants did not have deep brain stimulation surgery (DBS). PD participants were excluded from the study if they were experiencing any neurological (other than PD), or motoric

impairments that might impact their mobility, and if they were suffering from a cardiovascular disease, or other metabolic disorders. Participants were classified based on their weekly frequency of attending group exercise classes into a high – frequency group (n = 23; exercise 4-5 times/ week for 30 – 45 min. /bout), and a low – frequency exercise group (n=20; exercise dose ≤ 3 times/ week, 30 – 45 min. /bout).

Procedures. All participants were required to read and sign the University of Georgia Institutional Review Board (IRB) consent forms prior to beginning any testing and exercising. All participants completed two testing sessions scheduled one week apart prior to the exercise intervention, and one testing session at the conclusion of 12 weeks of exercise training. The effects of medication in PD participants was controlled by assessing and exercising the participants at 2 hours after medicine ingestion, which is the approximate peak of the medication effect (Ouchi, 2001). During the first session, the participants read and signed informed consent, completed a demographic and medical history questionnaire, took a screening test (Montreal Cognitive Assessment), and were trained to perform an Auditory Switch Task. Session two took place one week later and had three phases. First, all participants received retraining for both within- and between switch task category (60 trials each). Second, all participants were asked to complete a series of three Switch tests, which differed in the type of discrimination required and the number of stimuli presented. Two test types required within-category decisions (pure conditions): 200 number presentation (even/odd discrimination) and 200 letter presentation (consonant/ vowel discrimination). One test type required alternating-category decisions (mixed condition) made of 220 numbers and letters. Following the executive function task participants performed the Short Physical Performance Battery

(SPPB), a group of measures that combines the results of the preferred walking speed, chair stand and balance tests (J. Guralnik et al., 1994).

At the end of the 12 weeks of multimodal exercise intervention, all participants completed a systematic replication of session 2, performed with alternate forms of the switch task. A detailed description of the pre- exercise and post- exercise protocols for the cognitive task and SPPB is presented in the section below.

Measures

Cognitive Function Assessment

Auditory Switch Test. The first cognitive task was an auditory switch test designed to measure cognitive flexibility, a very important aspect of executive function (Miyake et al., 2000) In this assessment computer-generated letters or numbers were presented binaurally to a headphone via a commercial software program ("Cedrus. SuperLab.,"). The letters consisted of four vowels (A, E, I, and O) and four randomly selected consonants (B, D, L, and C). The numbers consisted four even numbers (2, 4, 6. and 8) and four odd numbers (1, 3, 5, and 7). The participant was required to respond to each stimulus by pressing a key on a regular size optical mouse (even number-left key; odd number-right key; vowel letter-left key; consonant letter-right key). Each key press was followed 100 ms later by the presentation of the next stimulus. Two types of block of trials have been used: in homogenous blocks, participants have been asked to respond to letters only or numbers only; in mixed or heterogeneous blocks, participants had to respond alternatively to letters and numbers. In mixed blocks, letters or numbers have been presented in series lengths of two, three or four stimuli. The letter-number category discrimination was switched following each series. In each block of trials, the initial 4

trials were considered practice and not evaluated. In the remaining we had discriminated between non-switch trials (i.e., repetitive within-category discriminations) and switch trials (i.e., a change in category discrimination), with an equal number of switches to even-odd and vowel-consonant conditions. Response times (RT) and response accuracy have been recorded for each trial.

After the training sessions, each participant performed a series of three tests, which were different in the type of discrimination required and in the number of stimuli. Two tests required within-category decision (pure condition): number presentation (even/ odd discrimination) or letter presentation (vowel/ consonant discrimination). One test type required alternating-category decisions (mixed condition) composed of both letters and numbers. All participants completed one 200 numbers-only test, one 200 letters-only test, and one 220 mixed-condition test. They performed the tests while seated in a quiet room and were instructed to respond as quickly and accurately as possible. Another series of tests with the same design have been applied after twelve weeks of multimodal exercise training. This is a protocol similar to the one used by Okumura, Cooper, Ferrara, and Tomporowski (2013).

Physical Function Assessment.

Short Physical Performance Battery

The Short Physical Performance Battery (SPPB) is one of the most common tools to measure physical performance in population studies on aging (Guralnik, Ferrucci, Simonsick, Salive, & Wallace, 1995). The SPPB captures a hierarchy of functioning from high levels of function to severe deterioration of lower-extremity function, with higher scores indicating better lower-body function. The SPPB is composed of three tasks: a

hierarchical balance task, a short walk at the usual speed, and five repetitive chair stands. Low scores in the SPPB have predictive value for a wide range of health outcomes: mobility loss, disability, and hospitalization, length of hospital stay, nursing home admission, and death (J. Guralnik et al., 2000; Penninx, 2000; Volpato et al., 2008).

For tests of standing balance, participants attempted to maintain the side – by – side, semi - tandem, and tandem positions for 10 seconds. Participants were scored 1 if they could hold a side – by – side stand for 10 seconds but were unable to hold a semi - tandem stand for 10 seconds, 2 if they held a semi - tandem stand for 10 seconds but were unable to hold a full tandem stand for more than 2 seconds, 3 if they held the full tandem stand for 3 to 9 seconds, and 4 if they held the full tandem stand for 10 seconds.

A usual pace, 8 – ft. walk was timed from a standing start, and participants were scored according to quartiles of performance. Time on the faster of two walks was used to define scores: score of 1: ≥ 5.7 seconds (≤ 0.43 m/s); score of 2: 4.1 – 5.6 seconds (0.44 – 0.60 m/s); score of 3: 3.2 to 4.0 seconds (0.61 – 0.77 m/ s); score of 4: ≤ 3.1 seconds (≥ 0.78 m/ s).

Participants were asked to fold their arms across their chest and to stand up once from a chair. If successful they were asked to stand up and sit down five times as quick as possible. Quartiles of performance for the repeat chair stands were used to define scores as follows: score of 1: > 16.7 seconds; score of 2: 16.6 – 13.7 seconds; score of 3: 13.6 – 11.2 seconds; score of 4: ≤ 11.1 seconds. A summary performance score was created by summation of the scores for tests of standing balance, gait speed, and rising from a chair 5 times.

Previous studies have shown high levels of correlation between the presence of some chronic conditions and lower levels of SPPB (Ferrucci et al., 2000) and high

predictive values of SPPB for disability, risk for mortality and nursing home admission (Guralnik et al., 1995; J. Guralnik et al., 2000; J. M. Guralnik et al., 1994). Also, in older acute care inpatients, SPPB is a valid indicator of functional and clinical status; SPPB score at hospital admission is an independent predictor of the length of hospital stay (Volpato et al., 2008).

Exercise protocol. The exercise protocol documentation was based on daily calendars recorded by all participants with the type, duration and perceived intensity of each activity. All subjects engaged in group exercise classes organized under the auspice of American Parkinson's Disease Association (APDA). The activity was consistent throughout all five senior centers located in Sandy Springs, Decatur, Roswell, Atlanta and Douglasville. The group exercise classes were conducted and recommended by two males and three females instructors certified by APDA and included aerobic activities such as: walking, running, stationary bike, water aerobics, water volleyball; resistance exercises with bands and dumbbells, and movement activities such as zumba and Tai Chi. Thus, the exercise intervention was mainly goal – oriented and focused on aspects of physical function specific to people with PD. The mean duration of the sessions was 42 minutes (±7 min.). The weekly amount of exercise that a participant reported was the criterion for classifying individuals into either the high – frequency group (4 - 5 times/ week), or the low - frequency group (≤ 3 times/ week). The dominant perceived intensity reported by participants in this study was moderate to heavy.

Statistical Analyses

Auditory Switch Task. Separate switch cost scores were calculated for tests composed of 200 and 220 trials. Global switch cost scores were calculated as recommended by Wasylyshyn et al. (2011). The average RT of the two pure, within-

category conditions (number and letter discrimination) was subtracted from the average RT of switch and non-switch trials in the mixed, between-category condition. For the correlation analyses we have determined the difference in performance following the exercise intervention by subtracting the global switch cost scores post – exercise from the pre – exercise ones.

Short Physical Performance Battery.

Summary performance scores for SPPB were calculated as recommended by Guralnik et al. (1994). Participants received a score from 0 (worst performance) to 4 (best performance) on each of the three individual tasks; the scores were then summed up to calculate the ordinal scores ranging from 0 (worst performance) to 12 (best performance). For the composite scores, an initial 2 (times) X 2 (groups) mixed factorial ANOVA with time as the within subjects factor was conducted to assess the changes in the overall physical function following exercise. Further, a 2 (times) X 3 (conditions) X 2 (groups) mixed factorial ANOVA, with time and condition as the within subjects factors, was performed to identify changes on each of the three tasks following the exercise intervention. In addition, linear regression was used to identify the relationship between the difference in executive function and walking speed pre – exercise and post – exercise. Analyses were conducted using SPSS 22 software ("SPSS IBM, New York, U. S. A.,"). The $p = 0.05$ rejection level was used in all analyses.

Results.

Short Physical Performance Battery.

Means of SPPB composite scores pre- and post- exercise are presented in Table 4.2, and in Graph 4.1. Results revealed a significant interaction between time and group,

F (1, 41) = 8.37, $p < .05$, $\eta_p^2 = 0.17$, suggesting a greater improvement in physical function for the high-frequency exercise group after the intervention. Post-hoc *t*-tests revealed that the two groups were not significantly different before the intervention, $t = 0.65$, $p = 0.51$, but differed significantly after the exercise training, $t = 4.40$, $p < 0.01$. Next, a mixed factorial ANOVA was performed with time and task as the within subjects factors. Means of SPPB scores for each independent task are presented in Table 4.3. and in Graphs 4.2., 4.3., and 4.4. Results revealed a significant interaction between task and group, F (2, 82) = 3.65, $p < 0.05$, $\eta_p^2 = 0.08$, suggesting that the high – frequency group performed better on each of the three physical tasks. Post-hoc *t*-tests indicated no significant difference at baseline for walking, balance and chair stands, and significant differences after the exercise intervention, balance: $t = 3.42$, $p < 0.01$; chair stands: $t = 2.11$, $p < 0.05$; walking speed: $t = 2.55$, $p < 0.05$.

Correlations.

Regression lines for the two exercise frequency groups are presented in Graph 4.5. A simple linear regression established that differences in walking speed following 12 weeks of high – frequency exercise could statistically significantly predict changes in global switch cost, $F(1, 21) = 25.921$, $p < .0005$ and walking speed differences accounted for 53.1% of the explained variability in global switch costs differences. The regression equation was: predicted global switch cost differences = -2.322 + 70.999 x (walking speed differences). As for the low – frequency exercise group, linear regression indicated that differences in walking speed after 12 weeks of low – frequency exercise could not statistically significantly predict changes in global switch cost differences, F (1, 18) = 3.404, $p = 0.082$ and walking speed differences accounted for 11.2% of the explained

variability in global switch costs differences. The regression equation was: predicted global switch cost differences = 8.511 + 24.400 x (walking speed differences).

Discussion.

The purpose of the present study was twofold: initially, to identify the effects of exercise frequency on the physical function in individuals with PD; and secondly, to analyze the relationship between changes in walking speed and changes in executive function following twelve weeks of exercise training in individuals with PD. Our findings indicate that individuals with PD that engage in multimodal exercise training at least four times a week, improve their physical function more than individuals with PD that exercise three times or less each week. Also, the correlation analyses performed suggests that alterations in physical function following a high - frequency exercise intervention could statistically significantly predict changes in executive function in people with PD.

For the physical function assessment, the Short Physical Performance Battery composed of three tasks: a hierarchical balance task, a short walk at the usual speed, and five repetitive chair stands was used, while executive function was measured with an auditory switch task designed to measure cognitive flexibility. Based on the initial analyses it was indicated that individuals with PD who engage in exercise training at least four times a week significantly improve their physical function compared to those individuals who participate three times or less. The significant interaction between task and group suggests that higher frequencies of exercise benefits each aspect of the physical function measured through the SPPB test when compared to lower frequencies of exercise. These findings indicate that changes in motor function in people with PD are dependent on exercise frequency intervention, and support previous studies by Fisher et

al. (2008) who also suggested a greater frequency and intensity in exercises interventions. Further, Fisher and colleagues (2008; 2007) indicated that exercise will positively influence and regulate the activity of brain circuitry responsible for the control of movement in individuals with PD, and supports our premise that cognition may be improved with exercise. Possibly, exercise can improve the dopamine signaling in individuals with PD, and increase blood flow in the brain (Muhlack, 2007). Increased blood flow will eventually augment the delivery of oxygen, help remove the waste materials, and accelerate the metabolic demands in the brain regions exposed to plasticity due to engaging in innovative experiences like exercise. These underlying physiological mechanisms support the benefits of exercise for improving overall functioning, and thus exercise should be an important component of treatment in PD.

Furthermore, data analysis also indicated an interesting association between changes in walking speed and changes in executive function following the exercise intervention program. The results of the high - frequency exercise group revealed a significant correlation between changes in physical and cognitive function, while the scores of the low - frequency group showed no significant relationship. These observations may indicate that alterations in physical function of people with PD following a high - frequency exercise intervention could statistically significantly predict changes in executive function. Although the correlation studies between physical and cognitive function in people with PD are lacking, our findings are consistent in comparison to older adults without PD. Weuve et al. (2004) suggested that long - term regular physical activity, including walking, is associated with significantly better cognitive function and less cognitive decline in older women which is also evident in this

study. We analyzed the correlation between walking speed and executive function since studies conducted by Guralnik et al. (2000) suggested that walking speed alone performed almost as well as the full SPPB battery in predicting incident disability community-dwelling populations.

In conclusion our study provides two noteworthy findings. First, the physical function benefits following a multimodal exercise intervention appears to be dependent on the frequency of weekly exercise, with high frequency triggering more extensive improvements. However, there is still a need to provide additional support for the optimal delivery and content of exercise interventions, and more precisely to determine the exercise types and dosage with the most promising effects on the physical function in people with PD. Our sample included individuals who had transportation problems and were reliant on caregivers' availability, so even the minimum amount of activity was helpful and could be supplemented with home programs to facilitate the frequency of the exercise program. Secondly, our results indicate that alterations in physical function of people with PD following a high-frequency exercise intervention could statistically significantly predict changes in executive function. We highlight the importance of future research focusing on the elucidation of the mechanisms underlying these associations. Answering these questions may point to new pathways for the treatment of physical decline associated with diminished cognitive function in individuals with PD. Finally, a qualitative assessment of all participants revealed that everyone felt better and more functional because of the exercise program. The psychological improvement may be an important part in dealing with a debilitating condition and loss of self – sufficient.

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Table 4.1. Demographic and clinical features of 43 patients with Parkinson's disease (PD).

Variable	HF exercise	LF exercise	p
Number of patients	23	20	
Male/ Female	16/7	10/10	
	mean (SD)	mean (SD)	
Age (years)	68.6 (5.8)	67.65 (4.5)	0.55
Age of PD onset (years)	57.5 (12.9)	58 (13.5)	0.62
PD duration (years)	10.6 (5.2)	9.8 (4.9)	0.83
Hoehn and Yahr	2.3 (0.5)	2.5 (0.4)	0.27
Education (years)	18.3 (2.9)	17.9 (2.7)	0.81
Exercise habits (times/ week)	5.1 (1.1)	2.2 (0.6)	< 0.0001*
MoCA score	25.5 (2.7)	25.4 (2.5)	0.88
UPDRS motor score	26.4 (4.3)	26.5 (5.0)	0.95

HF, high – frequency; LD, low – frequency; SD, standard deviation; MoCA, Montreal Cognitive Assessment; *significant difference ($p < 0.05$); UPDRS, Unified Parkinson's Disease Rating Scale.

Table 4.2. Short Physical Performance Battery mean composite scores by task, group and time.

Task	HD exercise		LD exercise	
	Pre-exercise	Post-exercise	Pre-exercise	Post-exercise
Walking	2.32	3.08	2.85	2.95
Balance	2.54	3.34	1.4	2.25
Chair	2.26	3.04	2.45	2.55
TOTAL	7.13	9.47	6.7	7.75

Table 4.3. Mean SPPB raw scores (s) (SD) by task, group, and time

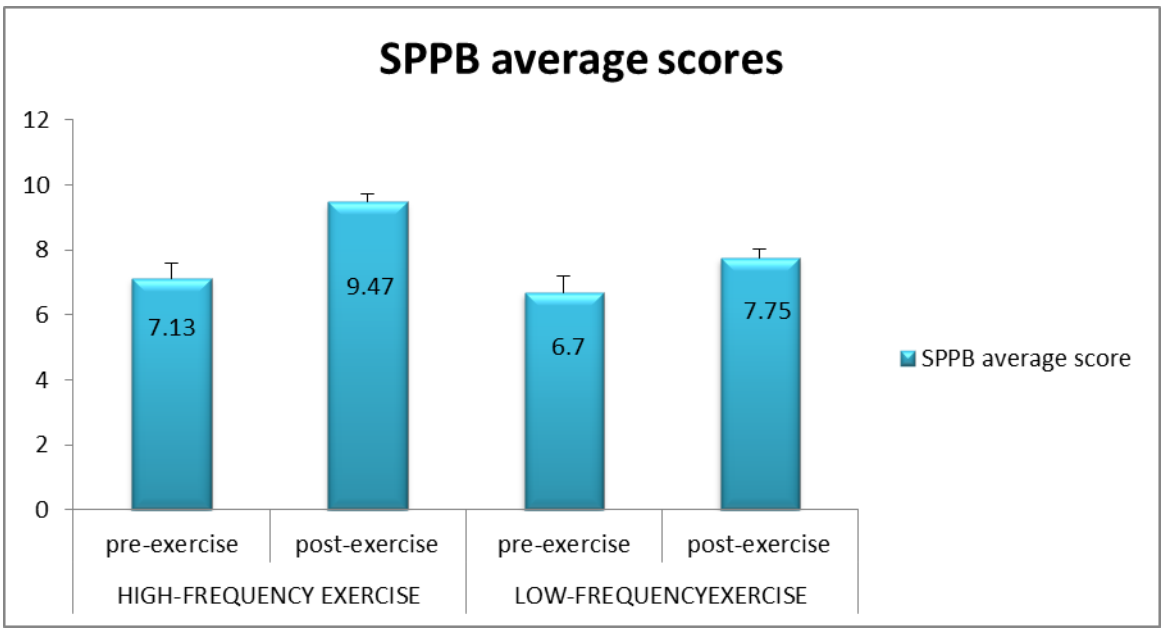
Task	HF exercise		LF exercise	
	Pre-exercise	Post-exercise	Pre-exercise	Post-exercise
Walking (s)	4.14 (0.75)	3.60 (0.58)	4.05 (0.57)	3.97 (0.52)
Balance (s)				
Side – by – side (s)	9.95 (0.2)	10	10	10
Semi – tandem (s)	8.52 (2.04)	9.86 (0.45)	8.3 (1.38)	9.15 (1.03)
Tandem (s)	6.56 (3.51)	8.30 (2.09)	5.65 (3.19)	7.05 (2.3)
Chair (s)	15.08 (3.95)	12.11 (2.14)	14.3 (2.98)	13.84 (2.25)

Table 4.4. Mean global switch cost scores (ms) (SE), by group and time.

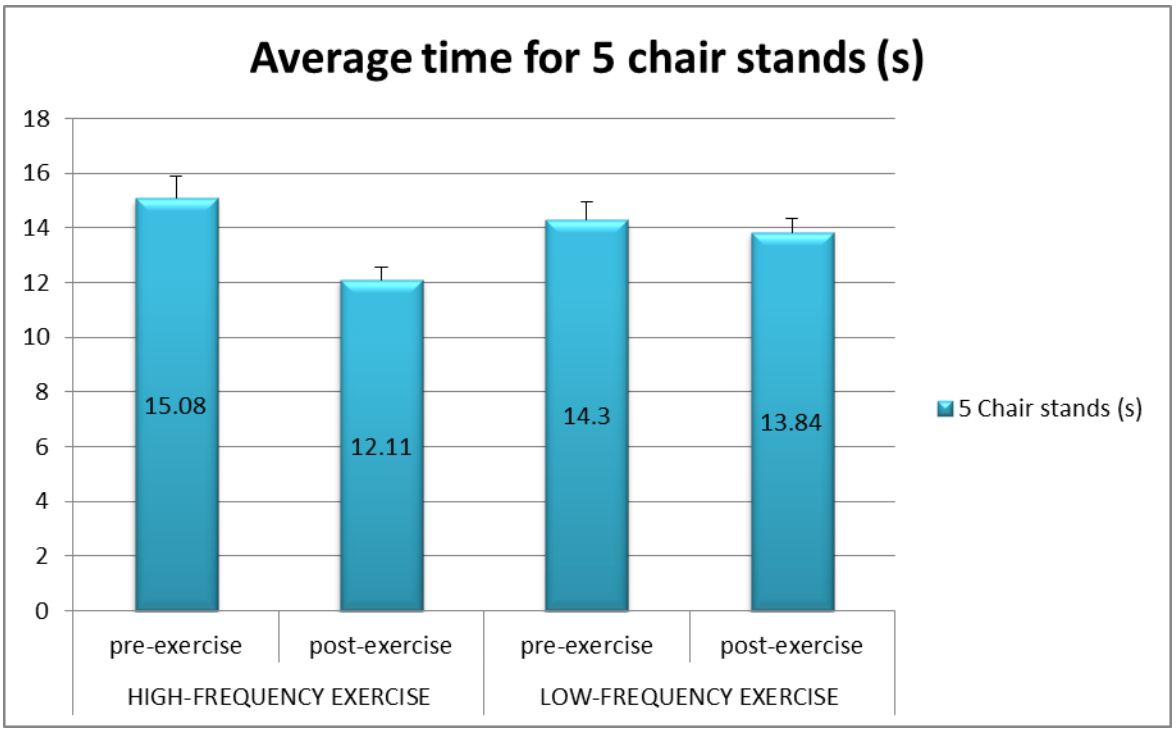
Condition	HF exercise	LF exercise
Pre-Exercise		
Switch-cost	139.48 (10.8)	140.15 (11.6)
Post-Exercise		
Switch-cost	110.81 (10.6)	143.72 (11.3)

HF, high – frequency; LF, low – frequency

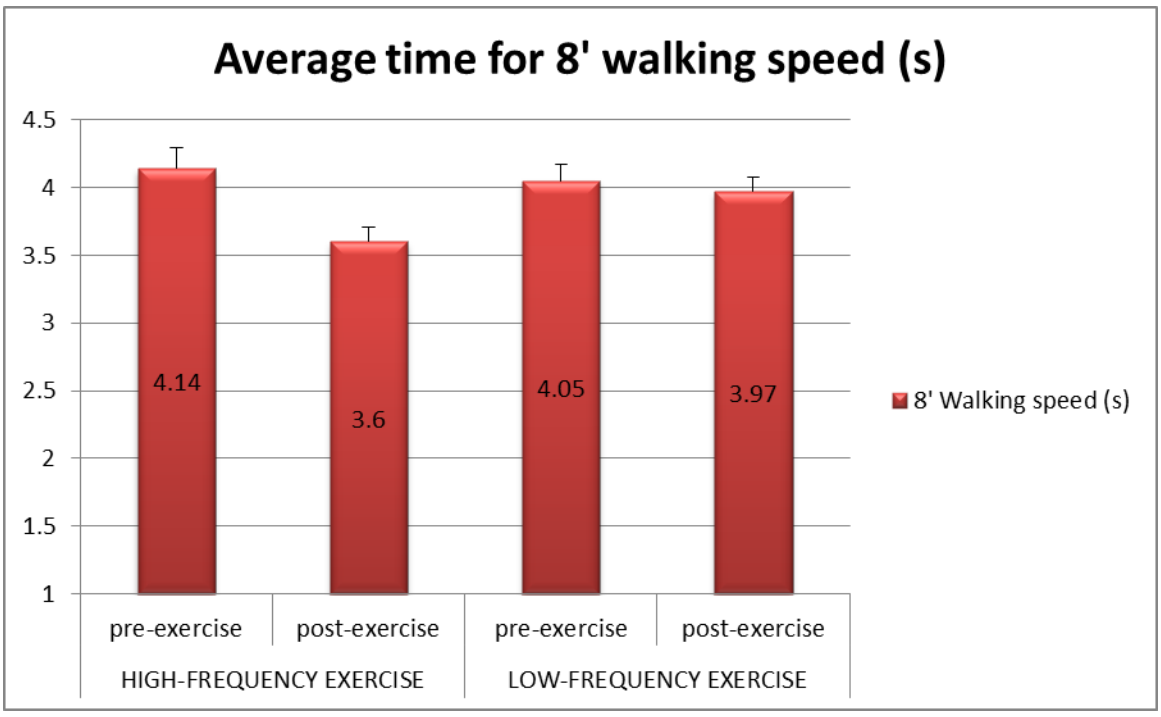
Graph 4.1. Mean SPPB composite scores and standard errors.



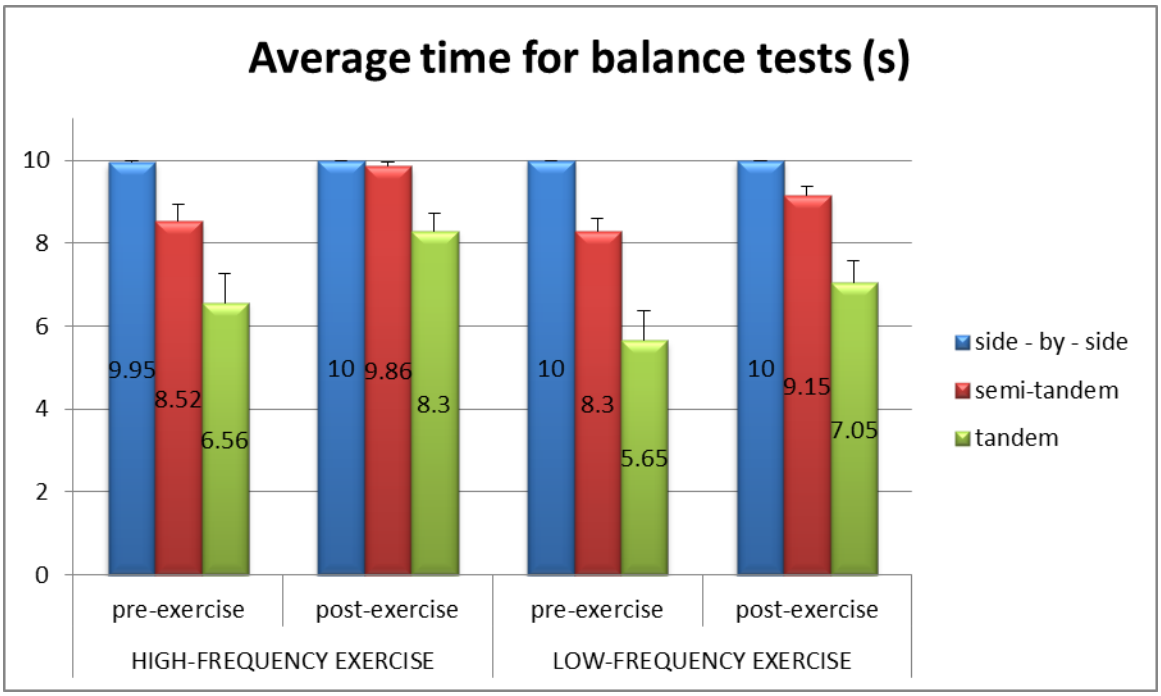
Graph 4.2. Mean time for chair stands(s) (SE).



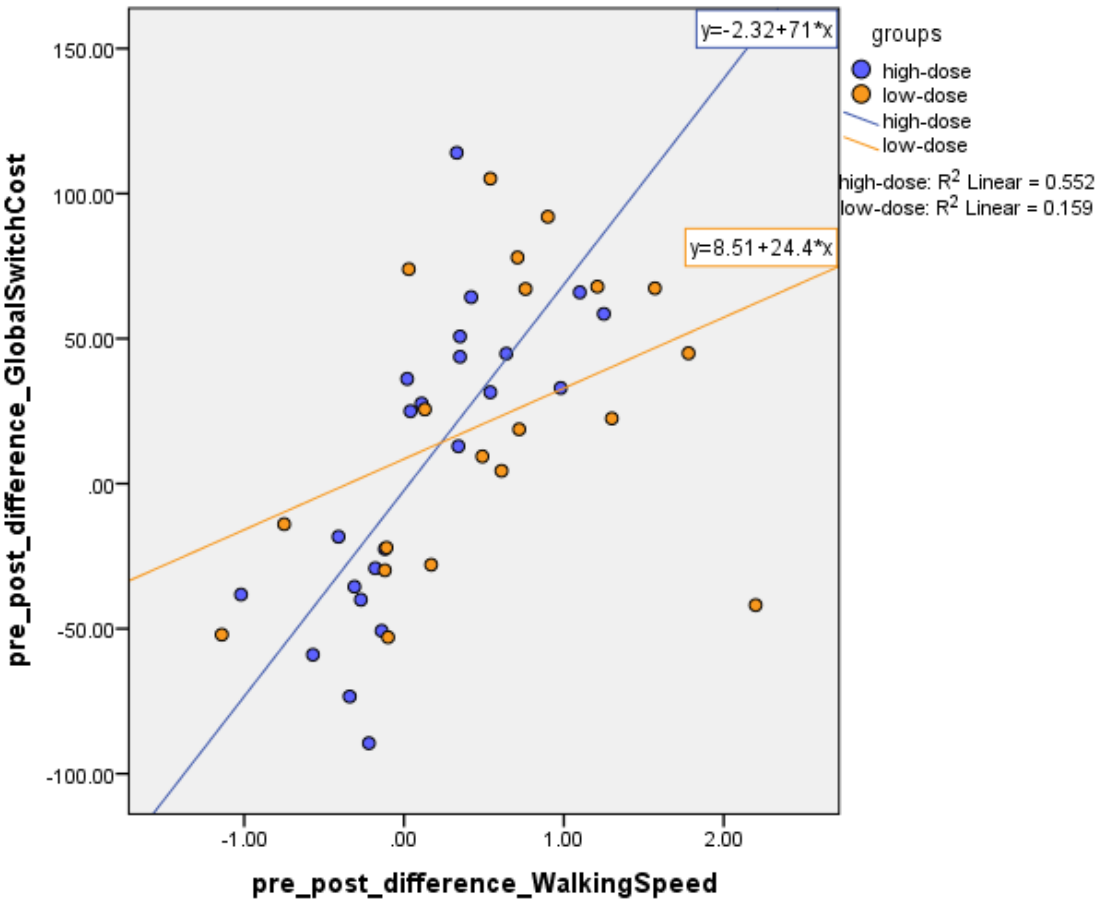
Graph 4.3. Mean time for preferred walk (s) (SE).



Graph 4.4. Mean time for balance task (s) (SE).



Graph 4.5. Regression lines for the correlation between walking speed and global switch cost by group.



CHAPTER 5

CONCLUSIONS

Parkinson's disease is characterized by a progressive loss of dopamine neurons, concentrated in the substantia nigra of the midbrain. The imbalance of chemical messengers in the brain results in tremor, akinesia, bradykinesia, postural instability and rigidity. Besides its typical symptoms, individuals with PD experience walking deficits, balance and posture alterations, muscular weakness and deconditioning. Other associated features are cognitive impairment and dementia which are as debilitating as the motor aspects of the disease. The main treatment option is levodopa taken in conjunction with medications that facilitate the transport and uptake of dopamine. Although these medications partially control and reduce the physical manifestations of the disease, they do not appear to benefit the cognitive aspects of PD. Exercise has been proposed as an adjunctive therapy for both physical and cognitive function in individuals with PD. However, the research on the benefits of exercise on the executive function in PD is only in its infancy, and there is still a need to identify the optimal delivery content, and the amount of weekly exercise with the most beneficial effects. Therefore we conducted two studies with the following purposes: 1) to identify the effects of different frequencies of multimodal exercise on selective aspects of executive function in non-demented individuals with idiopathic PD; 2) to determine changes in physical function in non – demented people with PD following 12 weeks of multimodal exercise training; and 3) to

examine the correlation between differences in walking speed and differences in executive function in PD after 12 weeks of exercise.

In the first study, individuals with early – moderate PD without dementia that exercised 4-5 times each week were compared to individuals with PD that exercised three times or less/ week. All participants completed two cognitive assessments designed to assess selective aspects of executive function, pre – exercise, and after 12 weeks of intervention. The major findings from this study indicated that: 1) high frequencies of weekly exercise are beneficial for cognitive flexibility in non-demented people with PD; 2) exercise benefits aspects of working memory in non-demented people with PD, with higher frequencies of exercise training exerting more benefits on people's RT than lower frequencies; 3) exercise, regardless of the weekly frequency improves response accuracy for both switching and working memory tasks in non - demented individuals with PD. Additionally intervention opportunities such as home – based programs should be encouraged to supplement our findings, while health care providers and policy makers should recommend exercise as part of routine management and neurorehabilitation for PD.

In the second study, PD participants were classified based on the reported weekly exercise habits into a high – frequency exercise group (exercise 4-5 times/ week), or a low – frequency exercise group (exercise $\leq$ 3 times/ week), and compared after 12 weeks of multimodal exercise training. They completed the Short Physical Performance Battery (SPPB), a test composed of three tasks: a hierarchical balance task, a short walk at the usual speed, and five repetitive chair stands; and the Auditory Switch task, a test designed to measure cognitive flexibility. The major findings from this study indicated that: 1)

individuals with PD that engage in multimodal exercise training at least four times a week, improve their physical function more than individuals with PD that exercise three times or less each week; and 2) alterations in physical function following a high - frequency exercise intervention could statistically significantly predict changes in executive function in people with PD. Future research should continue to provide additional support for the optimal delivery and content of exercise interventions, and more precisely to determine the exercise types and dosage with the most promising effects on the physical and cognitive function in people with PD.

The combined results from these studies indicate that changes in physical and cognitive function in in non – demented individuals with PD are dependent on a specific frequency of weekly exercise. Our results revealed that engaging in multimodal exercises for at least four times each week benefits selective aspects of executive and physical function, and also that changes in physical function can significantly predict changes in executive function following twelve weeks of exercise intervention in individuals with PD. Exercise for PD should continue to be promoted in community and home – based settings, and future research should focus on identifying specific intervention strategies that challenge the physical and cognitive capabilities of PD population at early and moderate stages of the disease. Also, health care providers and policy makers should recommend exercise as part of routine management and neurorehabilitation for PD.

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APPENDIX A

PARTICIPANT MEDICAL HISTORY AND DEMOGRAPHIC QUESTIONNAIRE

PARTICIPANT MEDICAL HISTORY AND DEMOGRAPHIC QUESTIONNAIRE

Name: _____

Date of Birth: _____

Address: _____

Phone number: _____

E-mail: _____

Blood Pressure: _____/_____

Height: _____ Weight: _____

Gender (circle) Male Female

Ethnicity (circle): Caucasian African American Hispanic Asian Other

Emergency contact name and number:

_____

Family Physician name and number:

_____

Please answer the following questions:

I. GENERAL HEALTH

1. Have you been diagnosed with dementia?

Y N

2. Have you ever been told by a physician that you have a heart condition?

   Y N

3. Have you or anyone in your immediate family had a heart attack, stroke, or cardiovascular disease before the age 50 years? If ~~"ye~~s", please explain.

   Y N

---

4. Have you ever been told by a physician that you have a high blood pressure?

   Y N

5. Have you ever been told by a physician that you have high cholesterol?

   Y N

6. Do you feel angina-like symptoms (pain or pressure in your chest, neck, shoulders, or arms) during or after physical activity?

   Y N

7. Do you ever lose your balance because of dizziness?

   Y N

8. Have you fallen in the last 12 months?

   Y N

   If ~~"ye~~s", how many times have you fallen: _____

9. Do you limit activity due to fear of falling?

   Y N

10. Do you ever lose consciousness?

Y N

11. Do you consider most of your days very stressful?

Y N

12. Do you consider your eating habits healthy overall?

Y N

(Lower in fats, and fried foods, higher in fruits, veggies and grains)

13. Have you been diagnosed with Parkinson's disease?

Y N

If ~~–ye~~s", when? _____

14. Are there any other health related issues we should know about?

Y N

Please explain_____

15. Have you ever been diagnosed with a depression?

Y N

If~~–ye~~s", please explain: _____

16. Have you ever been diagnosed with any additional mental health condition?

Y N

If~~–ye~~s", please explain_____

17. What hand do you use to operate the mouse on a computer?

RIGHT LEFT

Please make an "X" next to all that apply.

EARS: **NOSE:**

_____ hearing difficulty _____ bleeding

_____ringing _____difficulty smelling

_____pain _____nasal congestion

_____discharge _____sinus problems

_____other _____ other

Please explain

_____

PULMONARY:

_____ shortness of breath _____ chronic cough

_____wheezing _____allergies

_____asthma _____other

Please explain

II. MEDICATION/SUPPLEMENTS

1. Please list all of the **prescription medication** you are currently taking

Medicine name	Amount taken per day	Months/years on the Medication	Reason
a._____	_____	_____	
b._____	_____	_____	
c._____	_____	_____	
d._____	_____	_____	
e._____	_____	_____	

2. Please list all of the **over-the-counter medicines or supplements** (including vitamins) that you take regularly

---

EXERCISE HABITS

1. How many times per week do you generally exercise?_____

   a. What type(s) of exercise do you generally perform (circle all that apply)

      Walking Running Bicycling Swimming Weight lifting

      Aerobics Spinning Tennis Other

   b. In a typical week, how many days do you exercise? (circle)

      0-1 times/week 2-3 times/week 4-6 times/week

      daily

   c. How many minutes do you typically exercise per session (circle)

      <15 minutes 15-30 minutes 30-45 minutes >45 minutes

      Other_____

   d. What is the typical level of exertion during your exercise?

      Light Moderate Moderate/Heavy Heavy

III. PARKINSON'S DISEASE STATUS

1. What is your UPDRS motor score?_____
2. How long have you been diagnosed with Parkinson's disease?_____
3. When did you have your first PD symptom?_____
4. Has your physician ever discussed what type of PD you have?

   YES NO

   Idiopathic PARK Gene Alpha Syneuclin MPPT

   Other

5. Have you ever performed the Hoehn-Yahr Scale?

   YES NO

If yes, what is you Hoehn-Yahr Score?_____

6. Briefly describe your current PD symptoms._____
7. Do you fatigue easily?

   YES NO

8. Do you drive yourself independently?

   YES NO

9. Do you walk (circle) w/o aid with cane walker wheelchair
10. Has your physician ever recommended that you exercise?

    _____

IV. CURRENT EMPLOYMENT STATUS

1. Full time employed_____
2. Part-time employed_____
3. Retired_____
4. Not working_____

V. EDUCATION

1. None_____
2. Less that 8th Grade_____
3. High school incomplete_____
4. High school complete_____
5. College/Trade school incomplete_____
6. College/Trade school complete_____
7. Masters_____
8. Ph.D._____

9. Other_____

   Please explain_____

I certify that these answers are accurate and complete

_____ _____

YOUR SIGNATURE DATE

APENDIX B

PARTICIPANT EXERCISE CALENDAR

MY EXERCISE CALENDAR

OCTOBER 2013 PATIENT ID:

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURADAY
					25 Type*: Duration*: Intensity*:	**26** Type*: Duration*: Intensity*:
27 Type*: Duration*: Intensity*:	**28** Type*: Duration*: Intensity*:	**29** Type*: Duration*: Intensity*:	**30** Type*: Duration*: Intensity*:	**31** Type*: Duration*: Intensity*:		
Notes:						

Types of exercise: Walking, Running, Bicycling, Swimming, Weight Lifting, aerobics, Spinning, Tennis, Silver Sneakers (PD), Zumba (PD), Sited Exercises (PD), Tai Chi, Other (specify).

Durations: < 15 minutes; 15-30 minutes; 30-45 minutes; > 45 minutes.

Intensities: Light; Moderate; Moderate/ Heavy; Heavy.

MY EXERCISE CALENDAR

NOVEMBER 2013 PATIENT ID:

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURADAY
					1 Type*: Duration*: Intensity*:	**2** Type*: Duration*: Intensity*:
3 Type*: Duration*: Intensity*:	**4** Type*: Duration*: Intensity*:	**5** Type*: Duration*: Intensity*:	**6** Type*: Duration*: Intensity*:	**7** Type*: Duration*: Intensity*:	**8** Type*: Duration*: Intensity*:	**9** Type*: Duration*: Intensity*:
10 Type*: Duration*: Intensity*:	**11** Type*: Duration*: Intensity*:	**12** Type*: Duration*: Intensity*:	**13** Type*: Duration*: Intensity*:	**14** Type*: Duration*: Intensity*:	**15** Type*: Duration*: Intensity*:	**16** Type*: Duration*: Intensity*:
17 Type*: Duration*: Intensity*:	**18** Type*: Duration*: Intensity*:	**19** Type*: Duration*: Intensity*:	**20** Type*: Duration*: Intensity*:	**21** Type*: Duration*: Intensity*:	**22** Type*: Duration*: Intensity*:	**23** Type*: Duration*: Intensity*:
24 Type*: Duration*: Intensity*:	**25** Type*: Duration*: Intensity*:	**26** Type*: Duration*: Intensity*:	**27** Type*: Duration*: Intensity*:	**28** Type*: Duration*: Intensity*:	**29** Type*: Duration*: Intensity*:	**30** Type*: Duration*: Intensity*:
Notes:						

Types of exercise: Walking, Running, Bicycling, Swimming, Weight Lifting, aerobics, Spinning, Tennis, Silver Sneakers (PD), Zumba (PD), Sited Exercises (PD), Tai Chi, Other (specify).

Durations: < 15 minutes; 15-30 minutes; 30-45 minutes; > 45 minutes.

Intensities: Light; Moderate; Moderate/ Heavy; Heavy.

MY EXERCISE CALENDAR

DECEMBER 2013 PATIENT ID:

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURADAY
1 Type*: Duration*: Intensity*:	**2** Type*: Duration*: Intensity*:	**3** Type*: Duration*: Intensity*:	**4** Type*: Duration*: Intensity*:	**5** Type*: Duration*: Intensity*:	**6** Type*: Duration*: Intensity*:	**7** Type*: Duration*: Intensity*:
8 Type*: Duration*: Intensity*:	**9** Type*: Duration*: Intensity*:	**10** Type*: Duration*: Intensity*:	**11** Type*: Duration*: Intensity*:	**12** Type*: Duration*: Intensity*:	**13** Type*: Duration*: Intensity*:	**14** Type*: Duration*: Intensity*:
15 Type*: Duration*: Intensity*:	**16** Type*: Duration*: Intensity*:	**17** Type*: Duration*: Intensity*:	**18** Type*: Duration*: Intensity*:	**19** Type*: Duration*: Intensity*:	**20** Type*: Duration*: Intensity*:	**21** Type*: Duration*: Intensity*:
22 Type*: Duration*: Intensity*:	**23** Type*: Duration*: Intensity*:	**24** Type*: Duration*: Intensity*:	**25** Type*: Duration*: Intensity*:	**26** Type*: Duration*: Intensity*:	**27** Type*: Duration*: Intensity*:	**28** Type*: Duration*: Intensity*:
29 Type*: Duration*: Intensity*:	**30** Type*: Duration*: Intensity*:	**31** Type*: Duration*: Intensity*:				
Notes:						

Types of exercise: Walking, Running, Bicycling, Swimming, Weight Lifting, aerobics, Spinning, Tennis, Silver Sneakers (PD), Zumba (PD), Sited Exercises (PD), Tai Chi, Other (specify).

Durations: < 15 minutes; 15-30 minutes; 30-45 minutes; > 45 minutes.

Intensities: Light; Moderate; Moderate/ Heavy; Heavy.

MY EXERCISE CALENDAR

JANUARY 2014 PATIENT ID:

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURADAY
			1 Type*: Duration*: Intensity*:	**2** Type*: Duration*: Intensity*:	**3** Type*: Duration*: Intensity*:	**4** Type*: Duration*: Intensity*:
5 Type*: Duration*: Intensity*:	**6** Type*: Duration*: Intensity*:	**7** Type*: Duration*: Intensity*:	**8** Type*: Duration*: Intensity*:	**9** Type*: Duration*: Intensity*:	**10** Type*: Duration*: Intensity*:	**11** Type*: Duration*: Intensity*:
12 Type*: Duration*: Intensity*:	**13** Type*: Duration*: Intensity*:	**14** Type*: Duration*: Intensity*:	**15** Type*: Duration*: Intensity*:	**16** Type*: Duration*: Intensity*:	**17** Type*: Duration*: Intensity*:	**18** Type*: Duration*: Intensity*:
19 Type*: Duration*: Intensity*:	**20** Type*: Duration*: Intensity*:	**21** Type*: Duration*: Intensity*:	**22** Type*: Duration*: Intensity*:	**23** Type*: Duration*: Intensity*:	**24** Type*: Duration*: Intensity*:	**25** Type*: Duration*: Intensity*:
26 Type*: Duration*: Intensity*:	**27** Type*: Duration*: Intensity*:	**28** Type*: Duration*: Intensity*:	**29** Type*: Duration*: Intensity*:	**30** Type*: Duration*: Intensity*:	**31** Type*: Duration*: Intensity*:	
Notes:						

Types of exercise: Walking, Running, Bicycling, Swimming, Weight Lifting, aerobics, Spinning, Tennis, Silver Sneakers (PD), Zumba (PD), Sited Exercises (PD), Tai Chi, Other (specify).

Durations: < 15 minutes; 15-30 minutes; 30-45 minutes; > 45 minutes.

Intensities: Light; Moderate; Moderate/ Heavy; Heavy.

APENDIX C

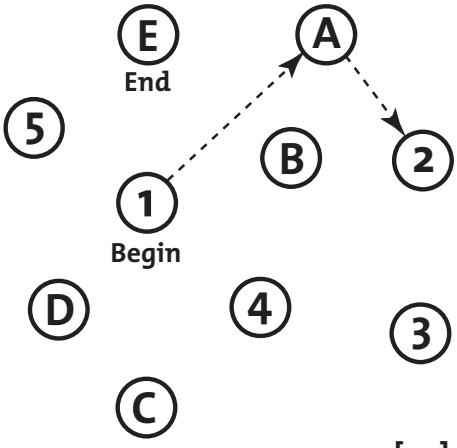
MONTREAL COGNITIVE ASSESSMENT (MoCA)

TEST AND INSTRUCTIONS

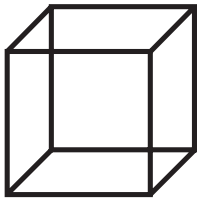
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



Copy cube



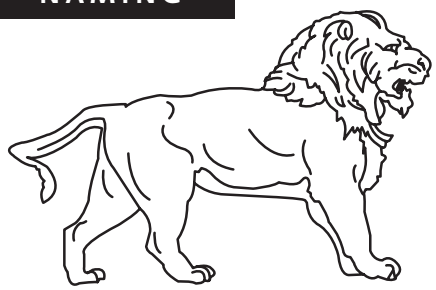
[ ] [ ]

Draw CLOCK (Ten past eleven)
(3 points)

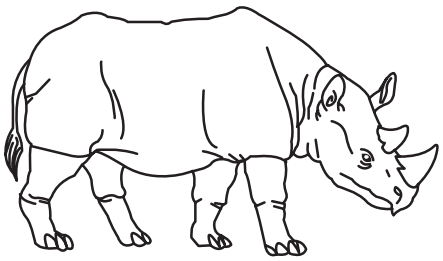
[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

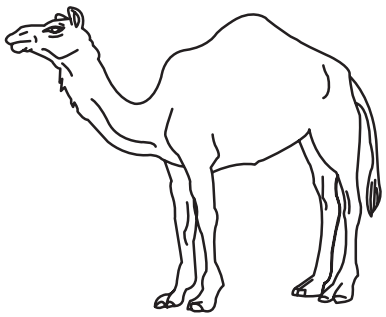
NAMING



[ ]



[ ]



[ ]

___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

___/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

___/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

___/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

___/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

___/6

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www.mocatest.org

Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

Montreal Cognitive Assessment

(MoCA)

Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. Alternating Trail Making:

Administration: The examiner instructs the subject: *"Please draw a line, going from a number to a letter in ascending order. Begin here* [point to (1)] *and draw a line from 1 then to A then to 2 and so on. End here* [point to (E)]."

Scoring: Allocate one point if the subject successfully draws the following pattern: 1 −A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. Visuo-constructional Skills (Cube):

Administration: The examiner gives the following instructions, pointing to the **cube**: "*Copy this drawing as accurately as you can, in the space below"*.

Scoring: One point is allocated for a correctly executed drawing.

• Drawing must be three-dimensional

• All lines are drawn

• No line is added

• Lines are relatively parallel and their length is similar (rectangular prisms are accepted)

A point is not assigned if any of the above-criteria are not met.

3. Visuo-constructional Skills (Clock):

Administration: Indicate the right third of the space and give the following instructions: *"Draw a **clock**. Put in all the numbers and set the time to 10 past 11".*

Scoring: One point is allocated for each of the following three criteria:

• Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g. imperfection on closing the circle);

• Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;

• Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centered within the clock face with their junction close to the clock center.

A point is not assigned for a given element if any of the above-criteria are not met.

4. Naming:

Administration: Beginning on the left, point to each figure and say: *"Tell me the name of this animal".*

Scoring: One point each is given for the following responses: (1) lion (2) rhinoceros or rhino

(3) Camel or dromedary.

5. Memory:

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions*: "This is a memory test. I am going to read a list of words that you*

will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn't matter in what order you say them".

Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s) he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: *"I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time."* Put a check in the allocated space for each word the subject recalls after the second trial.

At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, *"I will ask you to recall those words again at the end of the test."*

Scoring: No points are given for Trials One and Two.

6. Attention:

Forward Digit Span: Administration: Give the following instruction: "*I am going to say some numbers and when I am through, repeat them to me exactly as I said them*". Read the five number sequence at a rate of one digit per second.

Backward Digit Span: Administration: Give the following instruction: "*Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order.*" Read the three number sequence at a rate of one digit per second.

Scoring: Allocate one point for each sequence correctly repeated, (*N.B.*: the correct response for the backwards trial is 2-4-7).

Vigilance: Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: "*I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand*".

Scoring: Give one point if there is zero to one error (an error is a tap on a wrong letter or a failure to tap on letter A).

Serial 7s: Administration: The examiner gives the following instruction: *"Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop."* Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond "92 – 85 – 78 – 71 – 64" where the "92" is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

7. Sentence repetition:

Administration: The examiner gives the following instructions: *"I am going to read you a sentence. Repeat it after me, exactly as I say it* [pause]: ***I only know that John is the one to help today."*** Following the response, say: *"Now I am going to read you another sentence. Repeat it after me, exactly as I say it* [pause]: ***The cat always hid under the couch when dogs were in the room."***

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today;" substituting "hides" for "hid". altering plurals, etc.).

8. Verbal fluency:

Administration: The examiner gives the following instruction: *"Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready?* [Pause] *Now, tell me as many words as you can think of that begin with the letter F.* [time for 60 sec]. *Stop".*

Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject's response in the bottom or side margins.

9. Abstraction:

Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: *"Tell me how an orange and a banana are alike".* If the subject answers in a concrete manner, then say only one additional time: *"Tell me another way in which those items are alike".* If the subject does not give the appropriate response *(fruit)*, say, *"Yes, and they are also both fruit."* Do not give any additional instructions or clarification. After the practice trial, say: *"Now, tell me how a train and a bicycle are alike".* Following the response, administer the second trial, saying: *"Now tell me how a ruler and a watch are alike"*. Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:

Train-bicycle = means of transportation, means of travelling, you take trips in both;

Ruler-watch = measuring instruments, used to measure.

The following responses are **not** acceptable: Train-bicycle = they have wheels;

10. Delayed recall:

Administration: The examiner gives the following instruction: *"I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember."* Make a check mark (√) for each of the words correctly recalled spontaneously without any cues, in the allocated space.

Scoring: **Allocate 1 point for each word recalled freely without any cues.**

Optional:

Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (√) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, *"Which of the following words do you think it was NOSE, FACE, or HAND?"* Use the following category and/or multiple-choice cues for each word, when appropriate:

FACE: category cue: part of the body multiple choice: nose, face, hand

VELVET: category cue: type of fabric multiple choice: denim, cotton, velvet

CHURCH: category cue: type of building multiple choice: church, school, hospital

DAISY: category cue: type of flower multiple choice: rose, daisy, tulip

RED: category cue: a color multiple choices: red, blue, green

Scoring: **No points are allocated for words recalled with a cue.** A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be

improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

11. Orientation:

Administration: The examiner gives the following instructions: "Tell me the date today". If the subject does not give a complete answer, then prompt accordingly by saying: *"Tell me the [year, month, exact date, and day of the week]."* Then say: *"Now, tell me the name of this place, and which city it is in."*

Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, and office). No points are allocated if subject makes an error of one day for the day and date.

TOTAL SCORE: Sum all sub-scores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.

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APENDIX D

SHORT PHYSICAL PERFORMANCE BATTERY (SPPB)

Short Physical Performance Battery (SPPB)

1. Repeated Chair Stands

Instructions: Do you think it is safe for you to try and stand up from a chair five times without using your arms? Please stand up straight as quickly as you can five times, without stopping in between. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. Please watch while I demonstrate. I'll be timing you with a stopwatch. Are you ready? Begin

Grading: Begin stop watch when subject begins to stand up. Count aloud each time subject arises. Stop the stopwatch when subject has straightened up completely for the fifth time. Also stop if the subject uses arms, or after 1 minute, if subject has not completed rises, and if concerned about the subject's safety.. Record the number of seconds and the presence of imbalance. Then complete ordinal scoring.

Time: _____sec (if five stands are completed)

Number of Stands Completed: 1 2 3 4 5

Chair Stand Ordinal Score: _____

0 = unable

1 = > 16.7 sec

2 = 16.6-13.7 sec

3 = 13.6-11.2 sec

4 = < 11.1 sec

2. Balance Testing

Begin with a semitandem stand (heel of one foot placed by the big toe of the other foot). Individuals unable to hold this position should try the side-by-side position. Those able to stand in the semitandem position should be tested in the full tandem position. Once you have completed time measures, complete ordinal scoring.

a. Semitandem Stand

Instructions: Now I want you to try to stand with the side of the heel of one foot touching the big toe of the other foot for about 10 seconds. You may put either foot in front, whichever is more comfortable for you. Please watch while I demonstrate.

Grading: Stand next to the participant to help him or her into semitandem position. Allow participant to hold onto your arms to get balance. Begin timing when participant has the feet in position and lets go.

Circle one number

2. Held for 10 sec

1. Held for less than 10 sec; number of seconds held _____

0. Not attempted

b. Side-by-Side stand

Instructions: I want you to try to stand with your feet together, side by side, for about 10 sec. Please watch while I demonstrate. You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop.

Grading: Stand next to the participant to help him or her into the side-by-side position. Allow participant to hold onto your arms to get balance. Begin timing when participant has feet together and lets go.

Grading

2. Held of 10 sec

1. Held for less than 10 sec; number of seconds held_____

0. Not attempted

c. Tandem Stand

Instructions: Now I want you to try to stand with the heel of one foot in front of and touching the toes of the other foot for 10 sec. You may put either foot in front, whichever is more comfortable for you. Please watch while I demonstrate.

Grading: Stand next to the participant to help him or her into the side-by-side position. Allow participant to hold onto your arms to get balance. Begin timing when participant has feet together and lets go.

Grading

2. Held of 10 sec

1. Held for less than 10 sec; number of seconds held_____

0. Not attempted

Balance Ordinal Score: _____

0 = side by side 0-9 sec or unable

1 = side by side 10, <10 sec semitandem

2 = semitandem 10 sec.

4 = tandem 10 sec

3. 8’ Walk (2.44 meters)

Instructions: This is our walking course. If you use a cane or other walking aid when walking outside your home, please use it for this test. I want you to walk at your usual pace to the other end of this course (a distance of 8’). Walk all the way past the other end of the tape before you stop. I will walk with you. Are you ready?

Grading: Press the start button to start the stopwatch as the participant begins walking. Measure the time take to walk 8’. Then complete ordinal scoring.

Time: _____ sec

Gait Ordinal Score: _____

0 = could not do

1 = >5.7 sec (<0.43 m/sec)

2 = 4.1-6.5 sec (0.44-0.60 m/sec)

3 = 3.2-4.0 (0.61-0.77 m/sec)

4 = <3.1 sec (>0.78 m/sec)

Summary Ordinal Score: _____

Range: 0 (worst performance) to 12 (best performance). Shown to have predictive validity showing a gradient of risk for mortality, nursing home admission, and disability.

Reprinted from Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol Med Sci 1994; 49(2):M85-M94